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THE ETIOLOGY OF GRANULOPENIA (AGRANULOCYTOSIS)

With Particular Reference to Drugs Containing the Benzene Ring*†

ROY R. KRACKE AND FRANCIS P. PARKER

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In previous communications [11, 12, 13, 14] we have presented evidence to indicate that the chief etiologic factor in granulopenia is the administration of certain classes of drugs, particularly those which contain the benzene ring as their central nucleus. In June, 1931, before the American Society of Clinical Pathologists, we presented evidence tending to show that the injection of pure benzene is followed by clinical granulopenia in rabbits and also that the action of benzene on the hematopoietic tissue is more likely due to one of its oxidation products rather than to the drug itself. At that time we called attention to the fact that eight of the nine patients with granulopenia had been given large amounts of coal-tar benzene ring drugs prior to the clinical onset.

In 1931 one of us[11] published a report of a patient who had been given so much phenacetine over a three year period that she was admitted to the hospital with a severe methemoglobinemia and an acute fulminant attack of granulopenia. We[14] reported eleven cases of acute fulminant granulopenia in all of whom the clinical onset had been preceded by the administration of benzene ring drugs and presented the hypothesis that this disease is due mainly to the administration of that type of drug, attempting to formu-

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934. The Ward Burdick Award was made to Dr. Kracke for his work on granulopenia at the annual convention.

† This work aided by a grant from the Therapeutic Research Committee of the American Medical Association.

late a series of oxidation reactions in which it could be shown that these drugs can be oxidized to a common end product. We have called attention also to the high incidence of this disease in nurses and physicians and relatives of physicians and believe that this is brought about by the more common usage of these drugs in people of the medical group.

It is the purpose of this paper to present further evidence that our original conception of granulopenia was correct, and we propose to show; first, that granulopenia, based on a review of 1385 death reports, is a disease that affects nurses, physicians and medical people more than any group in this country; secondly, that certain drugs of the benzene ring class are capable of being easily oxidized to toxic products which are capable of producing granulopenia in rabbits.

Since our original communication on this subject the question of drug relationship to granulopenia has received confirmation from the important work of Madison and Squier[16] who reported fourteen cases of granulopenia; six of the patients had taken allonal, four amidopyrine, and the other four various drugs in combination with amidopyrine. They also showed that in six of these patients amidopyrine was used therapeutically after the onset of the disease and all of these died, while in the remaining eight, amidopyrine was prohibited and only two died. Furthermore, they were able to induce typical attacks of granulopenia by the administration of amidopyrine; on administering the drug to nineteen rabbits under variable conditions one animal developed granulopenia on the thirtieth day. This report apparently has stimulated many others to similar observations, for in the past few months Hoffman et al.[8] have reinvestigated their fourteen cases of granulopenia and found that thirteen of these patients had taken amidopyrine and that the onset in one was preceded by the administration of dinitrophenol. Randall[19] has reported the sudden development of granulopenia in a physician following the use of a barbiturate and amidopyrine. Zinninger[23] reported granulopenia in two sisters although she did not mention any association with drugs. At our request she later investigated the drug history and found that both of these patients had taken

large and undetermined quantities of amytal compound preceding the clinical onset.[24] Costen[4] reported three cases in which he stated his patients were women of "sedentary lives and nervous temperament," who required daily use of sedatives to obtain sleep and pointed out that one of his patients took large doses of aspirin, phenacetine and bromides; that another used allonal daily for several months, while the third was known to have taken large quantities of various sedatives.

The relation of drug therapy to granulopenia is being studied in Copenhagen, Denmark since Holten et al.[9] have reported five cases developing the disease while in the hospital being treated for other disorders, and in every instance had been given amidopyrine in the course of their treatment. They referred to a similar case by Videbech.[21] Andersen[2] reported a patient that had taken a mixture of amidopyrine and a barbiturate daily for five months and stated that his patient had recurrences following the administration of barbipyrine (compound containing amidopyrine), with recovery after the drug had been discontinued. Thus, at this time, there have been reported fifty cases of acute fulminant granulopenia in which various benzene ring drugs are incriminated as etiological agents with the chief interest centering on amidopyrine (see table 1).

Of these fifty patients forty-six have taken amidopyrine either alone or in combination with other drugs. Most of them have received the drug in combination with some form of barbiturate, while others have not received barbiturates. The onset of one was preceded by the administration of dinitrophenol[8] and in our series of eleven cases two had received large quantities of phenacetine; we reported one patient who took large amounts of acetanilid. However, this patient has since been reinvestigated and was found to have received amidopyrine also. We believe, therefore, that acetanilid can be ruled out as an etiological drug since there is no report of any case of granulopenia following the use of that drug alone. Since the publication of our last report we have seen a dentist with the acute fulminant type of the disease accompanied by complete loss of granulocytes, who had taken large quantities of phenacetine and we could not elicit any history of

TABLE 1

CASES OF GRANULOPENIA REPORTED WITH SUSPECTED DRUG ETIOLOGY

AUTHOR	CASE NUMBER	DRUG	
Madison and Squier	1	Allonal	
	2	Allonal	
	3	Allonal	
	4	Allonal	
	5	Allonal	
	6	Sodium amytal-amidopyrine	
	7	Amidopyrine	
	8	Neonal-amidopyrine	
	9	Amidopyrine	
	10	Amidopyrine	
	11	Amidophen-phenobarbital	
	12	Amidopyrine	
	13	Allonal	
	14	Amytal-amidopyrine	
Hoffman, Butt and Hickey	1	Amidopyrine	Some with and others without barbiturates
	2	Amidopyrine	
	3	Amidopyrine	
	4	Amidopyrine	
	5	Amidopyrine	
	6	Amidopyrine	
	7	Amidopyrine	
	8	Amidopyrine	
	9	Amidopyrine	
	10	Amidopyrine	
	11	Amidopyrine	
	12	Amidopyrine	
	13	Amidopyrine	
	14	Dinitrophenol	
Kracke and Parker	1	Peralga	
	2	Amidopyrine	
	3	Amidopyrine-phenacetine	
	4	Acetanilid	
	5	Amidopyrine	
	6	Various benzene drugs	
	7	Neoarsphenamine-phenacetine	
	8	Phenacetine	
	9	Phenacetine	
	10	Allonal-amidopyrine	
	11	Amidopyrine	
Randall	1	Amidopyrine-barbiturates	
Holton, Nielsen and Transbol	1	Amidopyrine	
	2	Amidopyrine	
	3	Amidopyrine	
	4	Amidopyrine	
	5	Amidopyrine	

TABLE 1—*Concluded*

AUTHOR	CASE NUMBER	DRUG
Costen	1	Aspirin-phenacetine
	2	Allonal
	3	Large quantity sedatives
Zinninger	1	Amytal compound
	2	Amytal compound
Pouzin-Malegue	1	Arsphenamine
Cassaute, et al.	1	Arsenobenzol
Lande	1	Solganol
Jacquelin and Allanic	1	Crisalbine
Achard, et al.	1	Solganol-crisalbine
	2	Solganol-crisalbine

administration of amidopyrine. It appears to us at this time that amidopyrine and phenacetine are incriminated in the production of this disease. Dinitrophenol might be added to these since this is a drug of the same class in so far as its benzene ring structure and oxidation potentialities are concerned.

There are a few references in the literature concerning the effect of drugs on the leukocyte count. Turley and Shoemaker[20] reported the effect of quinine and luminal on the leukocyte count, but since they gave only one grain of quinine daily to adults, the results would seem to be of little value. They also gave dogs two and a half grains of luminal daily for five weeks with a slight decrease of the leukocyte count during the first week. Nye and Barrs[17] found no effect on rabbits following the administration of amytal. More recently Watkins[22] has presented a brief summary of thirty-two cases of granulopenia from the Mayo Clinic and found that thirteen of these had received amidopyrine while eleven had received drugs of the barbiturate class, and in eight no history was obtained. In this connection, we would like to emphasize that obtaining an accurate history relative to the previous use of drugs in a patient with granulopenia is an extremely difficult task. In our experience, it is almost impossible to secure a history of any value from the relatives and friends of a patient who has long since been dead.

Hardwick and Randall[7] have studied the effect of pentobarbital

sodium on the leukocyte count of fifty-nine pregnant women and reported no depressing effect from this drug. It must be noted that these authors used a straight chain barbiturate and not a drug containing the benzene ring. It can be seen, therefore, that the available evidence points toward the incrimination of the benzene ring and the exclusion of the barbiturates. It is impossible to state at this time whether or not the action of the benzene ring drug is more effective by its combination with a barbiturate.

There are many reports in the literature of cases of granulopenia following the use of arsphenamine and neoarsphenamine, as the report of Cassaute et al.[3] in which a typical case developed following two injections of arsenobenzol, and that of Pouzin-Malegue[18] in which the disease developed after the administration of arsphenamine. It has long been known that arsenical preparations are capable of producing profound hematopoietic depressions. Most of these, however, are recorded in the literature under the diagnosis of aplastic anemia. There is ample evidence that in an occasional instance the administration of this type of drug produces a depression limited to granulocytes.

Concerning the combination of amidopyrine with the barbiturates, as seen in allonal and peralga, the Council on Pharmacy and Chemistry states that these are not chemical compounds but merely physical unions and mixtures of two drugs and that in all probability as soon as they reach the stomach they are broken down into their original components.

Relative to peralga, the Council on Pharmacy and Chemistry makes this significant statement,[5]

> If barbital or amidopyrine is placed in an oven at 100°C. no apparent change takes place; but when mixed fusion occurs such as happens in a depressed melting point determination, there is formation of yellow color and amine odor. In this manner there is formed a relatively small amount of a decomposition product, or probably products, not identified.

The above statement appears to us an important clue in the production of granulopenia and we submit evidence in this paper that this yellow product with an amine odor is an oxidation and

decomposition product and in all probability is quinone and that these products, when injected into rabbits, are capable of producing granulopenia. It would appear that there is no justification for combining amidopyrine, an analgesic, with barbital, a hypnotic, when there is evidence that dangerous toxic products are evolved in the process.

There have been reported cases of granulopenia that have arisen presumably following the administration of a class of drugs, commonly referred to as "gold salts," used in the treatment of tuberculosis. Reports of granulopenia following these drugs are quite common in France where they have the widest usage; Lande,[15] Jacquelin and Allanic,[19] Emile-Weil and Bousser,[6] Achard et al.[1] The report of the latter is of particular interest. These authors treated a patient with repeated injections of a gold salt known as crisalbine with no depression of the leukocyte count, which at this time was 11,400. This was followed by four injections of solganol with the leukocyte count dropping to 1200 with almost complete granulopenia. Another patient received ten weekly injections of crisalbine with no effect on the leukocyte count, but after receiving ten injections of solganol the count dropped to 2200 with complete granulopenia and death of the patient. This report is important since crisalbine does not contain the benzene ring, whereas solganol does contain the ring with the attached amine group, while both drugs contain the gold salt in its chemical structure.

As we have pointed out before,[14] the gold salts, arsphenamine, amidopyrine and phenacetine have certain structures in common, namely, the benzene ring with the attached NH_2, or amine group. This group merely facilitates the ease of oxidation. In the case of arsphenamine the benzene ring with the attached amine group is probably responsible for the leukocyte depression. It is of interest that most of these drugs were introduced about 1922 and have had their widest usage since that time, and granulopenia was first observed in the same year. Under the designation of amidopyrine, this drug has been on the market for twelve years. Phenacetine was introduced about twenty-four years ago. Empirin compound, a mixture of acetysalicylic acid, phenacetine and

caffeine, was introduced in 1923. Allonal was marketed in America in 1922 and peralga in the same year. The use of gold salts is comparatively recent. There are many other drugs that are in current use by the medical profession and by the laity that have this same essential structure, but are not mentioned in this paper since we confine our discussion only to those that have been reported as being causative in the production of granulopenia.

THE INCIDENCE OF GRANULOPENIA IN THE UNITED STATES WITH PARTICULAR REFERENCE TO OCCUPATIONAL STUDIES

In previous communications we have pointed out the apparent high incidence of this disease in physicians, nurses and medical people based on case reports in the literature. In order to verify this, we procured, from the United States Bureau of Vital Statistics, copies of the death reports of all cases under the heading of "agranulocytosis" and "agranulocytic angina" that were available. We were supplied with 1385 death certificates of this disease for the years 1931–32–33. Due to incomplete data seventy-one of these were excluded and our statistical studies are based on 1314 cases. A survey of the American literature reveals only 600 cases reported from 1922 to 1933. It is impossible to determine how many cases have occurred since this disease was first reported, but no doubt the number must run into the thousands. Furthermore, it is reasonable to assume that many patients have died with the diagnosis unrecognized.

Granulopenia had its first recognition origin at about the same time in Germany and the United States and probably occurs in about the same proportion in these two countries. We have pointed out before its rarity in England and this still remains true. It is of interest that many of the drugs have not had the wide spread and promiscuous use in that country as in the United States.

The disease, still remains one mainly of the white race; colored people rarely use the type of drugs that are incriminated in this list.

Table 2 shows the occupation distribution in the various groups. It is very evident from a study of this table that granu-

lopenia is far more prevalent among physicians, nurses, dentists, druggists, laboratory technicians, hospital orderlies, etcetera, than in any other group of people in the country. Although by far the largest number of cases are housewives, this group constitutes the largest population group but the rate of its occurrence in that group is 1.2 per hundred thousand as compared with 7.7 per hundred thousand of the medical population. We feel quite sure that the same figures will hold for relatives of physicians. The occurrence of the disease in members of doctors' families has been brought to our attention too often to be ignored.

TABLE 2

OCCUPATION

Occupational distribution per 100,000 population during 1931–1932–1933

Physicians	12.4
Nurses	8.5
Dentists	5.6
Druggists	2.9
Laboratory technicians	12.0
Hospital orderlies	5.0
Total medical group	7.7
Farmers	0.2
Lawyers	1.8
Ministers	2.0
School teachers	2.2
Stenographers	0.7
U. S. population as a whole	1.07
Housewives	1.2

In table 3 it can be seen that of the 236 death certificates of males in which the occupation was stated, physicians comprised the largest group and the same is true of nurses when housewives are excluded. For example, the condition is far more prevalent among nurses than among female school teachers and stenographers, and more prevalent among physicians than among lawyers and ministers. There can be little doubt but that the disease is prevalent among medical people and what ever theory of etiology receives final acceptance, in our opinion it must also explain this peculiar relation to the medical profession. We

have seen few physicians who do not have a package of allonal, amytal compound, peralga, or other such drugs lying on their desk within easy reach. It is easy for the doctor and certainly common practice when members of his family become ill to reach for one of these "newer and better drugs," with which he has been circularized and detailed. The same is true of the nurse in the course of her hospital duties.

TABLE 3

OCCUPATION AND SEX

Cases in which the occupation is stated (1314 cases)

Males		236
Physicians	19	
Dentists	4	
Druggists	2	
Hospital employees	5	
Laboratory technician	1	
Total medical group	37	
Total medical group	16%	
Females		159
Nurses	24	
Pharmacists	1	
Hospital employees	6	
Physician	1	
Total medical group	32	
Total medical group	20%	

OXIDATION OF DRUGS

It is our belief that the depressant action of this class of drugs on granulopoietic activity is due to one of its oxidation products and it is theoretically possible for all of these drugs to be oxidized to quinone. In a previous paper[14] we have presented this conception in detail and outlined an hypothesis illustrating the possible reactions by which the drugs of the benzamine group may be oxidized to the common end-product, quinone.

A series of experiments were designed to reproduce as nearly as possible the conditions of pH and temperature to which these drugs would be subjected in their passage through the upper

gastro-intestinal tract with the addition of a mild oxidative reaction. Certain barbiturates which were also oxidized under identical conditions served as controls.

Amidopyrine, phenacetine, acetanilid, acetylsalicylic acid, amytal and barbital, were each dissolved or suspended in 0.5 per cent HCl, in 0.5 per cent NaOH, and in neutral distilled water, incubated in a water bath at 40 to 45°C., and subjected to free flowing oxygen for periods of time varying from ten to thirty-

TABLE 4

DRUG SOLUTION	4 HOURS	12 HOURS	36 HOURS
Amidopyrine—0.5% HCl	Slate to Yellow	Deep Yellow	Amber
Amidopyrine—0.5% NaOH	None	None	None
Amidopyrine-neutral	None	None	None
Phenacetine—0.5% HCl	None	None	Yellow
Phenacetine—0.5% NaOH	None	Yellow	Intensified
Phenacetine-neutral	None	None	None
Acetanilid—0.5% HCl	None	None	None
Acetanilid—0.5% NaOH	None	None	None
Acetanilid-neutral	None	None	None
Acetylsalicylic—0.5% HCl	None	Violet (Needle crystals)	Violet
Acetylsalicylic—0.5% NaOH	None	None	None
Acetylsalicylic-neutral	None	None	None
Amytal—0.5% HCl	None	None	None
Amytal—0.5% NaOH	None	None	None
Amytal-neutral	None	None	None
Barbital—0.5% HCl	None	None	None
Barbital—0.5% NaOH	None	None	None
Barbital-neutral	None	None	None

six hours. Table 4 shows the color changes taking place with the approximate reaction time.

In those positive reactions indicated above, the yellow color was identical with that seen in a weak aqueous solution of quinone and there was a definite quinone odor in the flasks. The colored compound was soluble in ether and petroleum ether, and the impure crystals from these extractions turned brown on exposure to air at temperatures around 50°C. The yellow compound reacted easily with hydroxylamine to form crystals, which in the impure state melted at 119°C. (uncor.). Attempts to form 2-5 dianilinoquinone resulted in the production of a few red crystals, too scant in amount to obtain a melting point. Quinone titration with potassium iodide, sulphuric acid, and sodium thiosulphate showed the presence of a potassium iodide reducing substance in amounts

equivalent to approximately 0.0006 gm. of quinone per cubic centimeter of solution.

Spectrum analysis of a known solution of quinone in petroleum ether showed four absorption lines at 4960 Å, 4710 Å, 4575 Å, and 4360 Å which correspond to those given for quinone in hexane in the International Critical Tables. Similar analysis of a petroleum ether extract of an oxidized solution of amidopyrine showed two absorption lines occurring at 4673 Å and at 4422 Å in one sample, and at 4660 Å and at 4420 Å in a second sample. The darkest band in each case corresponded approximately with the darkest band in the known quinone solution.

A solution of James' tablets, a proprietary preparation which had been taken in large quantities by one of our patients, the formula of which could not be obtained, gave results identical with the above and indicated, therefore, that the essential component was amidopyrine.

The evidence given above, although not absolute, is strongly indicative that the yellow product formed by the mild oxidation of amidopyrine in weak acid solution and phenacetine in acid and alkaline solutions is quinone. The fact that amidopyrine oxidises much more easily than phenacetine probably accounts for the occurrence of the majority of cases of granulopenia resulting from amidopyrine administration, and the relatively few cases following phenacetine administration.

THE EFFECT OF OXIDATION PRODUCTS IN RABBITS

In a previous communication we have pointed out that benzene when given in small doses is capable of producing granulopenia in rabbits. We further pointed out that this action probably is not due to benzene as such, but to one of its oxidation products, and we have shown that such products as catechol can be recovered from the site of injection and from the bone marrow, whereas benzene is practically absent.

Three rabbits were injected twice daily with 1 cc. of a 25 per cent solution of paraaminophenol-hydrochloride in 5 cc. of normal salt solution for seventeen days, producing no effect on the leukocyte count.

A series of seventeen rabbits were injected with quinone. Eleven of these animals died on the first, second or third day from the immediate effects of the substance. Of the remaining six, two animals showed a complete granulopenia following the daily subcutaneous injections of quinone, one receiving 15 mgm. and the other 100 mgm. The third animal showed a marked depression of the

granulocyte count, whereas no effect was observed in the other three. In working with quinone we have noted that this is an extremely irritating and toxic substance and the chief experimental problem in the production of granulo-

TABLE 5

THE EFFECT OF DAILY SUBCUTANEOUS INJECTIONS OF QUINONE IN OLIVE OIL ON THE LEUKOCYTE COUNT OF RABBITS

100 MGM. DOSES		15 MGM. DOSES	
Date	Leukocytes	Date	Leukocytes
1934		*1933*	
3/27	4,950	11/13	12,600
3/28	16,150	11/14	13,850
3/29	9,100	11/15	8,650
3/30	5,500	11/16	10,950
3/31	5,850	11/17	9,200
4/1	2,250	11/18	8,900
4/2	4,200	11/19	5,950
4/3	5,350	11/20	7,950
4/4	3,300	11/21	7,200
4/5	1,550	11/22	5,900
4/6	2,050	11/23	2,850
4/7	1,900	11/24	4,050
4/8	1,750	11/25	6,900
4/9	2,400	11/26	7,450
4/10	2,950	11/27	6,300
4/11*	2,000	11/28	6,900
		11/29	7,500
		11/30	12,750
		12/1	6,000
		12/2	15,850
		12/3	4,050
		12/4	4,650
		12/5	3,950
		12/6	2,550
		12/10**	750

* Animal died with complete granulopenia.

** Animal died with complete granulopenia. In a series of six animals, three showed a marked granulopenia while three others showed little effect on the leukocyte counts.

penia appears to be the regulation of dosage in the individual animal so that an adequate amount is given for the production of granulopenia and yet the dosage remains sufficiently small so as not to kill the animal from its immediate effects.

Thus, we have noted that one animal may be able to tolerate a total dosage of 100 mgm. daily producing granulocytic depression, whereas the same dose would be fatal for another. Table 5 illustrates the effect of this drug on the leukocyte count.

Two animals were injected daily with 5 grains each of the following drugs for sixty days: allonal, barbital, phenacetine, acetanilid, amytal, aspirin and amidopyrine. All drugs were prepared by emulsifying with acacia and water and all

TABLE 6

THE EFFECT OF CATECHOL ON THE LEUKOCYTE COUNT OF RABBITS

Rabbit given daily intraperitoneal injections of 15 mgm. of catechol in 5 cc. of normal salt solution

DATE	LEUKOCYTES
1933	
11/13	6,350
11/14	9,850
	12,150
11/15	10,900
	12,950
11/16	10,800
	13,350
11/17	11,700
	13,900
11/18	5,450
	6,000
11/19	4,900
11/20	3,550
	3,200
11/21*	1,100

* Death. Two other rabbits showed a marked granulopenia while in three others the leukocyte count was little affected.

injections were intraperitoneal. In this series of fourteen animals we observed no depressant effect on the leukocyte count.

Three rabbits were injected daily with 1 cc. of a 25 per cent catechol solution producing granulopenia in two animals with 2000 cells per cmm. on the sixth and ninth days respectively. One animal was injected daily intraperitoneally with 15 mgm. of catechol in 5 cc. of normal salt solution producing complete granulopenia on the ninth day with death of the animal. Three other rabbits were injected subcutaneously with 15 mgm. of catechol daily, producing no depressant effect on the leukocyte count. Table 6 illustrates the effect of catechol in one animal in which granulopenia was produced.

In connection with our studies in granulopenia we wish to acknowledge our

indebtedness to the following members of the Emory University faculty whose help has been invaluable: Dr. Joseph Seifter of the Department of Pharmacology, Dr. O. R. Quayle, Department of Organic Chemistry, and Dr. Harris Purks, Department of Physics.

It appears to us that our failure to produce granulopenia by the injection of drugs as such, does not invalidate this conception of the etiology of granulopenia. It is logical to assume that rabbits as well as human beings have an adequate protective mechanism against the action of drugs of this class. This can be illustrated in the animal series of Madison and Squier in which only one of nineteen animals in which the dosage of allonal was so increased that in all probability the protective mechanism was over-whelmed, developed granulopenia. It can be readily seen that the injection of these drugs, whether it be subcutaneous, intraperitoneal or intravenous, would result in little opportunity for oxidation to the more toxic products, whereas the oral administration of the same drugs would, as we have already pointed out, lend them to easy oxidation in the gastro-intestinal tract. It will be noted that oxidation of amidopyrine was produced only in an acid medium. The reaction of tissues at the sites of injections are slightly alkaline. This probably accounts for our failure and that of other investigators to reproduce the condition by injecting this class of drugs. It appears that conditions necessary for easy oxidation in both the experimental animal and the human would be necessary for the production of granulopenia. As to what these conditions are is a problem that remains to be worked out in the future.

SUMMARY AND CONCLUSIONS

It seems that there is constantly increasing evidence that acute fulminant granulopenia and probably the chronic types as well are caused for the most part by the administration of easily oxidizable benzene ring drugs. In the literature there has now accumulated reports of fifty cases in which these drugs are incriminated; notably amidopyrine, occasionally phenacetine and in one instance dinitrophenol. These drugs have been taken with and without barbiturates of various types. So it appears

that barbiturates as a class have little or no effect in the production of the leukopenic state.

The evidence incriminating drugs in the production of this disease has become woven together in a strong chain of circumstantial evidence based on the history of the disease and the coincidental introduction of most of these drugs; based also on statistical data which clearly shows the prevalence of the disease among people of the medical group, obtained from a study of 1314 deaths in this country in the last three years; based also on the prevalence of the disease in Germany and the United States where these drugs have their widest use. We have been able to show that all of the cases of granulopenia under our observation have had drugs of this class prior to the clinical onset. Our studies in the oxidation reactions and the effect of oxidation products in animals indicate that quinone and perhaps catechol are the direct responsible agents in the production of this disease.

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DIAGNOSTIC METHODS IN AMEBIASIS*

Relative Value of Stool Culture as Compared with Other Methods

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The widespread occurrence of amebic dysentery and chronic amebiasis throughout the United States has aroused an intense interest in the disease among the members of the medical profession. Despite the fact that many surveys in the past have repeatedly pointed out the incidence of persons harboring *E. histolytica*, in one form or another, the extent of this disease in this country was not fully realized until quite recently, following the discovery of many cases having their origin in Chicago. The important and seriousness of this problem is vividly portrayed in the reviews of recent case reports which have shown the mortality rate in many instances to be extremely high.

Previous investigators have reported several outbreaks of amebic dysentery originating from a single case which was previously unsuspected and undiagnosed. Usually, the originating focus is found to be an "asymptomatic carrier" engaged as a food handler. Recognition, isolation and eradication of this disease from all infected individuals is the only means of combating this problem at the present time. This can be accomplished by a concerted effort on the part of all diagnosticians to render themselves more proficient in the available methods of examination.

Since the solution of the problem depends so much upon proper diagnosis of the condition, a comparative study of the usual diag-

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nostic methods was undertaken. Over a long period of time, various methods have been tried in the different types of cases and statistics kept on examinations of nearly 600 different specimens, including protoscopic aspirations, contents of liver abscesses, et cetera, from as many individuals. Far more examinations than here represented have been made, but comparative data in one phase or another have been kept in this series alone.

Clark[2] presented a series of 186 cases of amebiasis in which postmortem examinations showed the distribution of amebic lesions in the colon to be as follows: ulcers scattered throughout the colon, 60.7 per cent; ulcers only in certain regions, as cecum, ascending colon, sigmoid and rectum, 33.8 per cent; no definite intestinal ulcers, but scars and amebic lesions elsewhere in the body, 5.3 per cent.

The regions of the large bowel in their order of frequency of involvement, in both the acute and chronic cases, were found to be: cecum, ascending colon, rectum, sigmoid, and appendix. The transverse colon was rarely found to be involved.

Endamoeba histolytica, as its name implies, has definite cytolytic and hemolytic[5] properties which enable it to attack and successfully invade apparently healthy tissue. The lesions produced usually extend down through the muscularis mucosae and quite often penetrate through the wall of the intestine to the serosa. Usually the ulcer consists of a central necrotic core, surrounded by a reaction zone consisting of lymphocytes, plasma cells, endothelial cells and in the absence of marked secondary infection, relatively few polymorphonuclear leucocytes. Quite a few amebas can usually be seen in the necrotic core, many being easily demonstrable in the wall of the ulcer. Particularly, do the parasites collect around the walls of the necrotic vessels and not infrequently can be seen inside the lumen of the venules. This fact accounts for the frequent occurrence of complicating liver abscesses. These pathologic lesions are usually present in those cases having acute dysentery, the amebas being found in the stools and ulcers in the actively motile, vegetative stage.

In those cases which are usually referred to as chronic amebiasis

or so-called "asymptomatic carriers" the lesions simulate the above, but are very much less extensive; the degenerative and regenerative processes of the mucosal cells being in equilibrium, little or no dysenteric symptoms are produced. The stools of these chronic cases are usually formed and contain the resting or encysted stage of the *E. histolytica*. It is a curious fact and an experience which is not uncommon, that a specimen obtained one day will reveal relatively large numbers of cysts, while on succeeding days, only a few or maybe only one or two degenerated cysts can be demonstrated. Several days or even a week or two later, the stool will contain innumerable cysts again. These cycles of encystation, so to speak, must be borne in mind when examining stools from persons with either chronic or suspected amebiasis. At least two stools, collected at weekly intervals, should be examined in each case before the condition may be ruled out with a fair degree of assurance. Variability of clinical symptoms which these chronic cases present, many cases being completely asymptomatic, makes it impossible to determine the presence of infection from the clinical history or physical examination alone. Thus, the value of routine stool examination in all cases is self-evident.

Descriptions and differential diagnostic criteria of the various types and developmental stages of the pathogenic and non-pathogenic amebas may be found beautifully illustrated in any good textbook on parasitology or tropical medicine.

METHODS OF EXAMINATION

The cases have been divided into two large groups: (1) those cases having acute dysenteric symptoms in which active, motile, vegetative amebas were demonstrable in the ulcers of the bowel or in the liquid stools; (2) those cases not having acute symptoms, a number of which were asymptomatic, having no demonstrable ulcers in the lower bowel and rather formed stools which contained amebas in the encysted stage.

1. Methods of examination in cases of amebic dysentery

The examination of patients having acute dysenteric symptoms of amebiasis should consist of both proctoscopic examination of the rectum and lower sigmoid and complete stool examination, including the presence of blood, Charcot-Leyden crystals and flagellates.

A properly conducted proctoscopic examination will yield a great deal of information besides enabling one to examine directly the contents of the ulcers. In the majority of cases, no preparation of the patient is necessary. However, in some cases, a low enema, consisting of 500 cc. of normal saline solution may be given, allowing about fifteen to thirty minutes for the patient to expel it. Soap suds enemas, besides destroying many of the amebas in the bowel lumen, are irritating and further promote the already existing colonic spasm in the lower bowel which interferes with proper examination. The majority of cases will show considerable involvement of the lower part of the rectum; particularly, the plica transversalis recti, often referred to as Houston's valves. By using a small curet equipped with a long handle or a long piece of glass tubing (2–3 mm. bore), equipped with a rubber suction bulb, the entire contents of the ulcer wall may be obtained. The use of long cotton-tipped applicators usually does not give the best results. Diluting the material obtained from the ulcers with warm normal saline or Ringer's solution is advantageous in making a thin preparation. Direct examination on a glass slide under a cover slip, using a 16 mm. objective, will usually reveal large numbers of the organisms as irregularly quadrilateral, hyaline objects. Under higher magnification, the characteristic morphology and motility is usually easily demonstrable.

Diagnosis from direct stool examination in these cases when properly conducted is not difficult. A stool specimen examined at room temperature will reveal the amebas actively motile for thirty to forty minutes after passage from the bowel. The popular conception that the organisms will immediately cease their motility unless kept at body temperature is erroneous. This has led to the practice of placing the stool in warm water while being transported to the laboratory. It is not only unnecessary, but should the temperature of the specimen be raised above 43° to 47°C. the amebas will cease their motility, the high temperature and dehydration being quite detrimental. A search for amebas in the mucus and blood-streaked particles which come directly from the ulcers will usually reveal them in large numbers, except in cases which have received treatment in one form or another. Of particular note is the observation that bismuth, orally, will render the finding of *E. histolytica* in the stools quite difficult. The bismuth is usually present as the sulphide and identified under the microscope as black, irregularly rectangular crystals.

The presence of Charcot-Leyden crystals and intestinal flagellates with *E. histolytica* in stool specimens from acute amebic dysentery cases, has been pointed out many times before. We have demonstrated these in the majority of our cases.

Some staining methods for vegetative amebas require special technique and a great deal of time. Besides, a study of the motility of the amebas, which is so helpful in diagnosis, is not possible with these methods. For these reasons, although staining by iron-hematoxylin and alcoholic methylene blue methods are valuable for studying the nuclear structure, the simplicity of direct examina-

tion of unstained smears from freshly collected specimens makes this method far more practical.

2. Methods of examination in cases of subacute and chronic amebiasis

In this type of case it is usually the cystic stage of *E. histolytica* which is sought. It is an extreme rarity to find the encysted and vegetative stages in the same stool specimen. Sometimes, it is possible to demonstrate vegetative amebas in the bits of mucus which adhere to the surface of a semi-solid stool. However, the cysts which develop from the trophozoites in the lesions high in the colon, are usually found well mixed in the substance of the formed specimens.

The cysts of *E. histolytica* are more easily found in unstained, than in stained preparations. Unstained, under low magnification, they appear as tiny, practically colorless, hyaline, refractile, spheric bodies, easily distinguishable from the débris. Quite often they simulate tiny oil droplets, but are distinguished by their internal structure and staining characteristics. Some observers describe a greenish cast to cysts as seen under low power which aids in finding them on a slide. Under high magnification, the size, shape, thickness of the cyst wall, presence or absence of chromatoid bodies and other distinguishing characteristics, may be studied. However, detailed study of the number and structure of the nuclei requires staining by iodine, iron-hematoxylin or methylene blue.

By emulsifying a small bit of formed stool, the size of a pea, with a drop of water on a slide, it is possible, in heavily infested specimens, to find the cysts. However, concentration methods by centrifugation are easily performed in a few minutes and give a greater percentage of positive results. The simple dilution and concentration method [10] will give satisfactory results if the process of centrifugation is properly conducted. The cysts are well preserved and stain easily and subsequent cultures of these from the sediment is usually successful. This process also removes most of the bacteria and blastocystis, which overgrow the amebas in culture.

The method of Yorke and Adams[15] is useful in obtaining a good concentration of cysts, washing away most of the blastocystis and other bacteria. However, the method is more time consuming than the above and requires special glucose solutions. Primary cultures made from cysts concentrated by this method contains less contaminating bacterial growth, resulting in a more luxuriant primary culture of the amebas.

A method by which cysts may best be concentrated but one which we have found to be more especially adapted to concentration of the ova of intestinal parasites, has been recommended by De Rivas[7]. However, the acetic acid and ether so distort the morphology of the cysts that they appear granular, and the nuclear details are almost indistinguishable when stained. It apparently kills the majority of the cysts as successful cultures from the sediments are very difficult to obtain.

STAINING METHOD FOR CYSTS

As said above, a study of the nuclear structure of cysts requires special staining. By mixing the sediment containing the cysts with an equal part of Gram's or better, Lugol's iodine solution, a satisfactory staining of the nuclei is obtained. Thus, the presence or absence of glycogen bodies, the number of nuclei and situation of the karyosome, all practical distinguishing characteristics, is easily determinable. The technique of this stain is simple and the staining solutions are always available in every laboratory.

McDaniels[12] recently recommended a saturated solution of methylene blue in methyl alcohol as a stain for vegetative and encysted amebas. Although the method gives fair results, we have found that it had no advantage over the iodine stain.

The iron-hematoxylin technique for staining cysts gives excellent results and detailed study of cysts is made possible. However, the special solutions, special technique and length of time required by the procedure, makes this method more adaptable to research than to practical diagnosis. It was also found that the number of cysts seen after completion of the stain, was far less than the number seen in comparative preparations unstained. Apparently, in the process of fixing and staining the wet smears, many of the cysts are mechanically washed off the slide. We have encountered only exceptional cases which required staining by the iron-hematoxylin technique in order to determine the type of organisms present.

CULTURAL METHODS

Boeck and Drbohlav[1] introduced the egg-serum-Locke's medium, consisting of a coagulated egg base superimposed by inactivated blood serum diluted with Locke's solution. This medium gave uniformly satisfactory results and successfully demonstrated the fact that *E. histolytica* was not an obligatory tissue parasite. The addition of acriflavine and rice starch* to the superimposed serum-Locke's or serum-Ringer's solution, introduced by Dobell and Laidlaw,[8] was a distinct advantage. Craig[4] then introduced a simple Locke's-serum medium which proved useful for perpetuating an already existing culture of trophozoites. He also demonstrated the fact that a base is not absolutely essential to propagation of *E. histolytica*. In an effort to retain the simplicity of the Locke's serum medium and add to its efficiency, St. John[13] introduced a similar medium composed of heart muscle extract and Locke's solution to which wheat flour was added. Other modifications have been reported from time to time which have proved of value. Recently, a liver infusion agar-serum-Ringer's-rice starch combination medium was described by Cleveland and Collier.[3] This medium still retains the essential principles embodied in the original Boeck and Drbohlav medium, the liver infusion agar is substituted for

* Rice starch prepared by Eli Lilly & Co. (Lilly's authentic starches).

the egg base, the superimposed liquid being composed of Locke's-serum-rice starch.

After a preliminary survey, the following cultural methods were selected and an endeavor made to determine their comparative simplicity and initial cost of preparation, practicability and efficacy, as regards positive results during routine examination for vegetative and encysted amebas: (a) Egg-serum-Locke's medium of Boeck-Drbohlav, (b) Egg-serum-Ringer's medium of Boeck-Drbohlav, (c) Egg-serum-Ringer's-rice starch, acriflavine medium of Dobell-Laidlaw, (d) Loeffler's-serum-Ringer's-rice starch-acriflavine medium of Dobell-Laidlaw, (e) Heart muscle-Locke's-wheat flour medium of St. John and (f) Liver infusion-agar-serum-Ringer's-rice starch of Cleveland-Collier.

Method of inoculating and examining cultures. From the cases of acute amebic dysentery, fresh stool specimens or material from the ulcers through a proctoscope or both, were obtained; one or two drops being immediately inoculated directly into two tubes of each of the culture mediums listed above. Only two tubes were used in order to determine the practicability of the method. Certainly, should more than two tubes be inoculated, the chances of obtaining positive cultures are greater, but the practicability of the method is thereby reduced.

At twenty-four to thirty-six hour intervals, the material from the surface of the base, or in the case of St. John's medium, the sediment at the bottom of the tube, was skimmed off with a capillary pipette equipped with a Wright's rubber bulb. The pipette had a large lumen (1 mm.) and its end was broken off squarely after scratching with a small file. The drop of material was placed on a slide, cover glass applied and examination made with the 16 mm. objective. The growth of amebas reached their maximum in twenty-four to forty-eight hours, varying slightly according to the culture medium used (see fig. 1).

The formed stool specimens from routine cases and those suspected of having chronic amebiasis were handled in a similar manner at first. It was soon evident, however, that better results were obtained when the specimen was diluted and concentrated before planting. The washing of the specimen removes the bulk of the bacteria and the majority of the blastocystis, besides concentrating the cysts. A large drop of this washed and concentrated sediment was inoculated into two tubes of each of the medium used. Examination of the cultures was performed as above. The maximum growth of the amebas when specimens containing cysts were inoculated was approximately forty-eight to ninety-six hours (see fig. 2).

Examination of the cultures as described above is not difficult. The amebas retain their motility for approximately one hour at room temperature after removal from the incubator.

The number of trophozoites in a slide preparation from a primary culture of cysts varies considerably. In general, the more cysts inoculated into the medium the more trophozoites are obtained, but exceptions to this are frequently en-

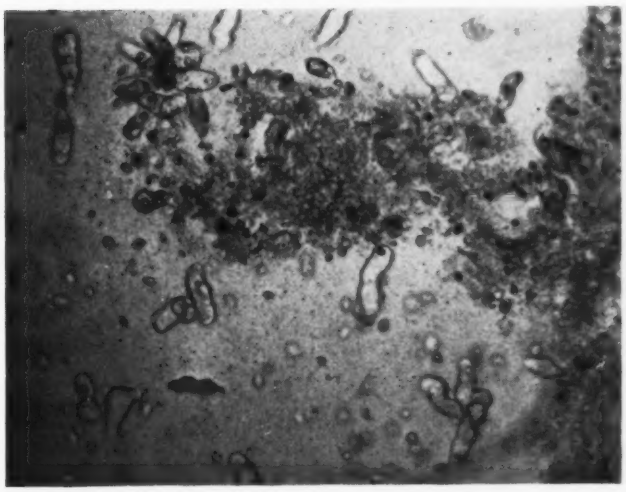

FIG. 1. AVERAGE FIELD SEEN IN SLIDE PREPARATION

E. histolytica trophozoites from twenty-four to forty-eight hour primary culture of vegetative forms from rectal ulcers of acute case of amebic dysentery.

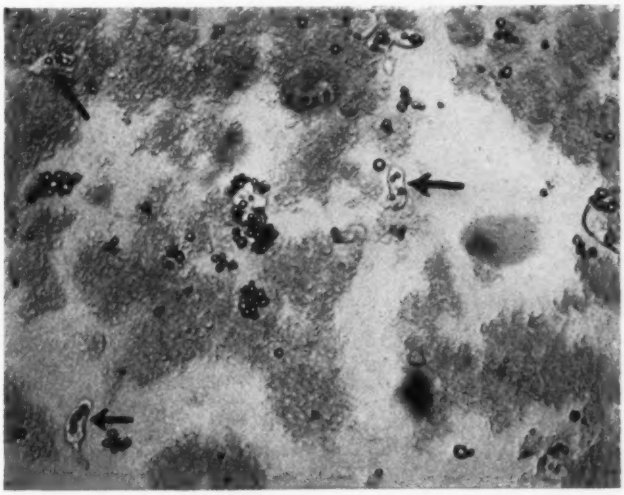

FIG. 2. AVERAGE FIELD SEEN IN SLIDE PREPARATION

E. histolytica trophozoites (arrows) from forty-eight hour primary culture of stool specimen which contained many cysts from "carrier" of amebiasis.

TABLE 1

EFFICACY OF THE MORE COMMONLY USED CULTURE MEDIUMS AS COMPARED WITH SIMPLE SMEAR AND CENTRIFUGE CONCENTRATION METHODS IN SPECIFIC CASES*

NUMBER OF CASES	DOBELL-LAIDLAW MODIFICATION OF BOECK-DRBOH-LAV, EGG BASE	DOBELL-LAIDLAW MODIFICATION OF BOECK-DRBOH-LAV, LOEFFLER'S BASE	ST. JOHN'S HEART MUSCLE LOCKE-SERUM WHEAT-FLOUR NO BASE	LEVELAND-COLLIER MODIFICATION OF BOECK-DRBOHLAV LIVER-AGAR BASE	REMARKS
Suspected amebiasis, negative for *E. histolytica* by direct examination					
7	−	−	−	−	Cases of previously proved and treated amebiasis.
5	−	−	−	−	Only cysts, morphologically *E. coli* and *E. nana*, present by direct microscopy.
3	−	−	−	−	Cases of chronic bacillary dysentery.
2	+	−	−	−	Only cysts, morphologically *E. coli*, *E. nana* and *I. buetschlii*, present by direct microscopy.
2	+	−	−	+	Only cysts of *E. nana* present by direct microscopy.
1	+	−	−	−	Case of proved amebiasis. Specimen of 3rd day after specific treatment started. Negative by all methods thereafter.
1	+	−	−	−	Only one atypical cyst in sediment by direct microscopy.
Amebiasis, positive for trophozoites of *E. histolytica* by direct examination					
1	+	+	−	− (Gas production due to bacterial growth)	St. John's media 3 mos. old. Cleveland-Collier media unsatisfactory; "blew up" due to gas. Subsequent batches O.K.
4	+	+	+	+	New St. John's and Cleveland-Collier media used.
Amebiasis, positive for cysts of *E. histolytica* by direct examination					
1	−	−	−	− (Gas, etc.)	Specimen 3 days old before culture.
4	+	+	−	− (Gas, etc.)	
4	+	−	−	− (Gas, etc.)	
1	+	−	−	−	New batch of Cleveland-Collier medium.
4	+	−	−	−	New batch of Cleveland-Collier medium.

* Two tubes of each medium inoculated in a single attempt. From nearly 600 patients, including previous work, 41 specimens containing cysts characteristic of *E. histolytica*, successful cultivation in Dobell-Laidlaw or Cleveland-Collier modification medium was possible in all cases when sufficient cultures (as many as ten) were made from as many as three different specimens.

countered. Sometimes, only one or two trophozoites are seen on an entire slide; other cultures from other cysts may show ten to twenty trophozoites per field of a 16 mm. objective.

Further details of preparation of media, inoculation and examination may be found in a previous report by one of us.[14]

RESULTS

A comparison of results obtained in the majority of representative specimens is shown in table 1.

DISCUSSION

Many controversial statements may be found concerning the value of cultural methods as compared with direct examination of stools for *E. histolytica*. Indeed, even as regards the different modifications of culture mediums in use, the opinions vary as regards the efficacy of each one. Some investigators[3, 6, 9, 11] say that for routine use, it is superior to direct microscopy and others that it is inferior.

Vegetative amebas, either from an untreated acute case or previous culture, when inoculated into any of the mediums used in this series, will be propagated indefinitely under proper care. The Dobell-Laidlaw and Cleveland-Collier Mediums give the most luxuriant growth on primary culture. However, St. John's medium, although less efficient as regards primary culture and luxuriance of growth, has the advantage of simplicity of preparation and less bacterial growth. The carbohydrate of the large particles of wheat flour is not easily available and consequently growth of blastocystis is inhibited to a remarkable degree. This medium is most useful in propagating stock cultures of amebas.

The morphology of the trophozoites of *E. histolytica* as seen in culture is not remarkably changed from those seen directly in the stool or from the ulcers. Of course, erythrocytes are no longer present in the endoplasm, but their place is taken by starch granules from which the organisms derive their food supply. The amebas grown on St. John's medium are smaller in size than those from the other mediums, and their motility is less characteristic, but the other morphological characteristics are still retained.

The Cleveland-Collier medium is a little more costly to prepare than the others. Some batches of it have proved totally unsatisfactory, due to the fact that bacterial action upon the base produced gas, which caused the whole tube of media to "blow up," so to speak. In a few instances, the base was almost completely extruded from the tube, resulting in loss of the culture. However, other batches have not shown this same phenomenon and have proved satisfactory. Possibly, aging of the ingredients was responsible although we purchased the material fresh and used it in a short time. Perhaps, some change in the preparation of the ingredients during manufacture may account for the unsatisfactory results at times.

The Dobell-Laidlaw modification is cheaply prepared and all ingredients are readily available, no purchase of materials or time for delivery being necessary. The rice starch may be kept indefinitely. This medium has proved to be superior to the others used in this work and may well be advocated as a practical, efficient diagnostic aid in routine work.

Initial primary cultures from *E. histolytica* cysts are not as uniformly successful as with the trophozoites. Cysts in specimens not over twelve to twenty-four hours old result in more successful cultures than older cysts. Several specimens contained cysts which failed to excyst in the initial culture in the two tubes of one or the other of the mediums. We believe that should sufficient tubes be inoculated, positive cultures will be obtained from all fresh specimens containing cysts.

The cultural methods used are practically specific for *E. histolytica*. This is an advantageous feature of the cultural method in identifying cysts. The other amebas usually do not excyst and grow. In a few instances, *E. coli* and *E. nana* trophozoites may be found. They retain their morphological characteristics but, unlike *E. histolytica*, do not engulf starch. On subculture, the *E. coli* and *E. nana* trophozoites die out; in contrast to *E. histolytica*, which becomes more prolific with each subculture. In some of the cultures of *E. histolytica* which have been transplanted many times, the growth is so luxuriant that slide preparations show every field of the microscope literally crowded with amebas.

The stool specimens from two cases contained cysts morphologically like *E. coli*, *E. nana* and *Iodamoeba buetschlii*, as identified by direct examination. However, on culture typical trophozoites of *E. histolytica* were found and confirmed by subculture through many generations. Apparently, a few *E. histolytica* cysts were present, but not identified by direct examination.

In one case by direct examination, only one cyst could be found in the entire examination. The identification in such cases is extremely difficult. Careful study and staining may be practically impossible for a very few cysts. Cultivation of the sediment will usually add a great deal of information for identification of species.

Some small strains of *E. coli* cysts and some large strains of *E. nana* cysts in feces may so closely simulate unstained *E. histolytica* cysts morphologically that positive identification without staining is difficult.

The vegetative stage of *E. coli* in cancerous or syphilitic ulcers of the rectum may simulate the trophozoites of *E. histolytica* in that they may engulf red blood cells under these conditions. An error in diagnosis may be avoided if subsequent studies of the organisms in culture be performed.

The study of the vegetative forms and cultural characteristics of the three intestinal amebas more commonly encountered in practice, in addition to the study of the encysted stage, gives sufficient information to identify the organisms in the majority of cases. These studies at least give as much information and is less time-consuming and more practical than the study of iron-hematoxylin stains.

The cultural methods are practical and may be used in the average laboratory without any additional cost. The technique is not any more difficult than that required for routine bacteriological work. In general, the results of a worker just beginning to use cultural methods in diagnosis are usually not remarkably inferior to one who has been using the method for a long time. The technique is easily mastered in a short time. Certainly, as compared with learning special techniques, such as iron-hematoxylin and differential criteria of stained cysts, the method is simpler, less time-consuming and cheaper.

The complement fixation test of Craig[5] for the diagnosis of amebiasis has not been sufficiently developed to render it available for routine use. The results obtained are not conclusive enough to make it a reliable method as yet. However, improvements are constantly being made and the future possibilities of the test are encouraging.

The use of alcohol-glycerin-saline extracts of luxuriant cultures of *E. histolytica* as an antigen for skin tests has been used by one of us (C. J. T.). Extraction of all the bacteria also occurs and consequently non-specific reactions interfere with proper interpretation of the results. Until amebas can be grown in pure cultures in the absence of all bacteria, satisfactory extracts for skin testing will be difficult to obtain.

SUMMARY AND CONCLUSIONS

(1) A comparative study of the various diagnostic methods used in acute and chronic amebiasis is presented.

(2) Stool specimens and contents from rectal ulcers of acute cases have been studied for *E. histolytica* trophozoites in fresh unstained smears, iodine, methylene blue and iron-hematoxylin stained smears and by various cultural methods.

(3) In acute cases, examination of fresh unstained smears and subsequent cultures of the material have been found to be the most practical and efficient procedures.

(4) In chronic or suspicious cases, stool specimens were examined for cysts by direct smears, concentration methods, iodine, methylene blue and iron-hematoxylin stains and cultural studies.

(5) A most practical and efficient procedure of examining stools for cysts is the simple water dilution and centrifuge method. Staining the cysts with Lugol's iodine solution will satisfactorily reveal the nuclei. Subsequent culture permits study of the trophozoite stage of *E. histolytica*.

(6) The Dobell-Laidlaw modification of the Boeck-Drbohlav medium was found to be the most practical and efficient cultural method in routine examination of material for trophozoites and cysts of *E. histolytica*.

(7) A study of the vegetative forms and cultural characteristics

of the three more common intestinal amebas, in addition to a study of the encysted stage, gives sufficient information for practical identification in the majority of cases.

(8) The cultural methods for *E. histolytica* are practical and may be used in the average laboratory without any additional cost or special training.

We wish to thank Mr. C. C. Adams of this department for his valuable technical assistance throughout this work.

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RAPID PIGMENT APPEARANCE IN OHIO RED BELLIED DACE AS TEST FOR INTERMEDIN*

Preliminary Report

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Zondek and Krohn[5] in 1932 demonstrated conclusively that the hormone regulating pigment metabolism is elaborated by the pars intermedia of the hypophysis. Furthermore, they found a small fish native to Germany (the elritza) an ideal test object for the demonstration of the effect of the hormone since the adult male with silvery undersurface (except in the spawning season) when injected with a small amount of an extract of the intermediate lobe of the hypophysis quickly developes a specific brilliant red coloration. They named the hormone intermedin and found no excess of the hormone in the blood or urine of man in health or in disease.

After a year's unsuccessful attempts to secure a supply of elritza from Germany, a search was made of the literature of domestic fish. Impressed by the similarity of the red bellied Minnow (*Chrosomus erythrogaster*) of Ohio (Jordon[3]) with the elritza, a supply of the former was obtained in March 1934. It was found that this minnow, also known as the Ohio red bellied dace, reacts beautifully after the injection of material containing intermedin, the reaction appearing within one half hour and persisting for four to twenty-four hours.

The first important work relating to pigment metabolism was that of Hogben and Winton[1] who reported on the action of posterior pituitary extracts on the melanophores of frogs. They stated that the hormone controlling pigment metabolism was most abundant in the intermediate lobe. The results of Hogben

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934.

and Winton in frogs were confirmed by Allen and Atwell but it remained for Zondek and Krohn to introduce the ideal test animal. Since the work of Zondek and Krohn, Ferguson[2] (1933) using imported elritza as the test object found a demonstrable amount of intermedin in the blood of patients having melanosarcoma and neurogenic sarcoma.

The red bellied minnow measures 5 to 8 cm. in length (same size as elritza). In the spring the males have a bright red belly. Their habitat is the clear brooks from the Ohio valley to the Red River of the North. They differ from the elritza in having a rounded rather than a flat body. The upper surface of the body of both male and female is of an olive drab color. The fish when first isolated from the stream require an environment simulating that of their natural habitat as closely as possible, but may be gradually adapted to the conditions of the ordinary aquarium and as supplied by the dealer thrive on prepared foods. The most essential requirement is the maintanance of live water plants in the aquarium to absorb harmful substances, such as chlorine. Under proper conditions the fish may be bred in the aquarium, the local dealer depending almost entirely upon this source of supply.*

As stated above, the male dace reacts beautifully to intermedin. During the spawning season, May and June, when the water is warm (about 20°C.) the male fish spontaneously develops a flame colored pigmentation of the under surface of the body. By keeping the water in the aquarium cold (about 15°C.) the pigmentation disappears and with properly controlled temperatures the fish may be used as test objects during this season.

Saphir[4] has reported on "Artificial Production of 'the Wedding Dress' in *Chrosomus Erythrogaster*" commonly called red bellied dace. He obtained positive results with yohimbine hydrochloride and inconstant results with prolan as isolated from the urine

* Wm. Tricker, Inc., Independence, Ohio and Saddle River, New Jersey. We wish to express our appreciation to Mr. J. L. Charlesen, Manager of the Independent Plant, for helpful suggestions as to maintaining the life of the fish in the aquarium.

of pregnant women. He also obtained a positive result with urine extract of a case of chorionepithelioma.

The work presented in this preliminary paper was done with a few hundred red bellied dace obtained since March. A study was made of the behavior of the fish to injection of intermedin, other hormones, and urine of patients in health and with various diseases.

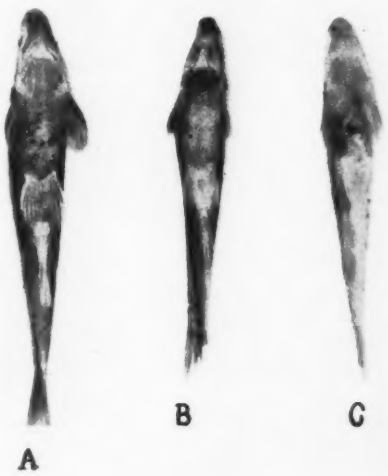

FIG. 1. PHOTOGRAPH OF RED BELLIED DACE

A. Strongly positive result in a case of melanosarcoma of the eyeball. B. Spontaneous pigmentation in the spawning season. C. Negative control. The dark ventral surfaces of A. and B. are actually a flame red color. Ventral surface of C. is actually silvery.

TECHNIC OF THE TEST

In general the technic of the test is as described by Zondek and Krohn[5] in the elritza. Healthy adult male fish measuring 6.5 to 7.5 cm. in length are selected. The fish are held in a wet cloth in the left hand and a fine hypodermic needle attached to a 1 cc. (tuberculin) syringe is inserted just back of the dorsal fin for a distance of about 1 cm. to avoid leakage of the material injected. The injection is made just beneath the skin to avoid penetrating the air bladder of the fish. The volume of the material injected varies from 0.1 to 0.3 cc., small doses being better tolerated. After injection, the fish are placed in individual

glass bowls for observation. The dace tolerate the necessary manipulations out of water well.

Except in the spawning season, the male fish has a silvery under surface. In a positive test, the under surface develops a brilliant flame red color apparently due to rapid elaboration of pigment as shown by Zondek's[7] demonstration that four and a half times as much red pigment can be extracted from the deeply pigmented skin as from the unpigmented controls.

Zondek defines one elritza unit of intermedin as the minimum amount of hormone in which three out of five elritza (6.5 to 7.5 cm. long) produces about the

TABLE 1

RESULTS OF TESTS WITH VARIOUS HORMONES IN RED BELLIED DACE

HORMONE	STRONGLY POSITIVE	POSITIVE	DOUBTFUL	NEGATIVE
Posterior pituitary extract	10			
Anterior pituitary extract	8			
Corpus luteum		2		1
Amniotin			2	1
Theelin			1	
Antuitrin S				1
Prolan				1
Androtin		1	3	
Parathormone		1	1	1
Epinephrin				1
Insulin				1
Thyroxin				1
Thyrovarian				1
Adrenal extract				1
Mixed gland (male)				1
Mixed gland (female)				1

mouth, breast, abdomen, and from the anal fin back to the anus, in an area 4 to 9 sq. mm. large, a striking formation of light purple red color. The reaction must begin within one half hour and lasts for four hours.

In the red bellied dace, it has seemed advisable to consider as a doubtful reaction one in which there is an appearance of one or more small areas of pigmentation measuring less than 4 sq. mm. in diameter anywhere on the undersurface. A positive reaction consists in a streak of red pigmentation extending along each side of the body from the buccal fin back to the anal fin. A strongly positive reaction consists in a brilliant pigmentation of the entire undersurface of the body. These changes must appear in two out of three injected fish.

RESULTS

Strongly positive results were obtained with extracts of the posterior lobe of the ox pituitary which also includes intermediate lobe. Extracts of the anterior lobe were also positive probably

TABLE 2

RESULTS OF TESTS FOR INTERMEDIN IN RED BELLIED DACE

DIAGNOSIS	MATERIAL INJECTED	POSITIVE	FALSE POSITIVE	DOUBTFUL	NEGATIVE
	Ringer's solution with 0.25 per cent acetic acid				2
	Physiological saline				3
Melano-sarcoma, eyeball	Urine conc. 5 ×	1 (Pre-op.)			1 (Post-op.)
Neurogenic sarcoma	Urine unconc.	1 (Pre-op.)		1 (Post-op.)	3 (Post-op. and post X-ray)
Various clinical conditions other than neurogenic sarcoma and melanosarcoma	Urine conc. 5 ×		2		11
	Unconc. urine		2		27
Hydatid mole					1
Pregnancy					1
Negro					2

due to postmortem diffusion of intermedin into the anterior lobe. Weakly positive results were obtained with corpus luteum extract, amniotin and theelin. Variable results were obtained with androtin and parathormone. Negative results were obtained with the other hormones tested. (See table 1.)

As the pituitary extracts were made up in 0.25 per cent acetic acid, control fish were injected with Ringer's solution containing 0.25 per cent acetic acid and with physiological saline solution. These tests were uniformly negative. In a case of neurogenic sarcoma the urine of which was given us through the courtesy of Dr. F. Bayless of the Institute of Pathology, Western Reserve University, a positive result was obtained preoperatively, a doubtful result postoperatively, and three negative results following X-ray therapy. In a case of melanosarcoma of the eyeball a positive result was obtained five days after removal of the eyeball and a negative result subsequent to removal of the remaining orbital tissue which on microscopic examination showed a small amount of tumor tissue. In a series of thirteen tests in which the urine was concentrated according to the method* described by Zondek[6] two false positive results were obtained.

In a second series of twenty-nine cases in which unconcentrated urine was injected, two false positive results occurred. Tests done with urine from two negroes were negative. Table 2 shows results of injection of urine in various clinical conditions.

A number of urines, both concentrated and unconcentrated, were toxic and the fish died before sufficient time had elapsed for reading the test.

Additional experiments are under way to determine the specificity of the dace as a test object for the demonstration of intermedin.

CONCLUSIONS

There is a rapid red pigment appearance in the Ohio red bellied dace similar to that in the elritza following injection of extracts and urine containing intermedin.

In the small series of tests so far completed, positive results were also obtained with urine from one case of melanosarcoma and one case of neurogenic sarcoma. Non-specific results with urine,

* Add to the urine to be tested an equal quantity of 95 per cent alcohol and concentrate to one-tenth the volume by evaporation on the water bath thus concentrating the urine five times. (Intermedin, unlike the hormones of the anterior lobe of the pituitary, is not destroyed by boiling.)

however, have occurred in a few cases apparently unrelated to these tumors.

A large series of experiments will be necessary to determine whether or not the positive reaction in the red bellied dace is a reliable index of the presence of intermedin.

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ENDOCARDITIS CAUSED BY DIPHTHEROID BACILLUS (PLEOMORPHIC STREPTOCOCCUS)*

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For many years the tendency of most workers has been to consider diphtheroid bacilli obtained from human sources, especially from blood cultures as contaminants or as mere saprophytes. This view in general is taken by the British Medical Research Council[5] in their summary of the literature up to 1923. However, some have considered these organisms to be of pathogenic significance. Recently Kessel and Romanoff[10] fairly completely summarized the literature in regard to infections by diphtheroid bacilli and described a non-fatal case of generalized infection, including meningitis, in which four blood cultures and the spinal fluid revealed diphtheroid bacilli.

No case of endocarditis has yet been described in which diphtheroid bacilli have been found alone in the heart vegetations. Tow and Wechsler[16] found in smears of the heart vegetation of a child of eleven who had been sick from endocarditis for six weeks, many diphtheroid organisms and a few Gram positive cocci, singly or in pairs. No cultures of the valve were made. From three cultures of the blood a diphtheroid bacillus which grew abundantly on ordinary media and which had the characteristics of *Corynebacterium hoffmanni* was obtained. It produced methemoglobin in forty-eight hours on blood agar. They believe that the streptococcus found in smears was the etiologic agent and that the diphtheroid bacillus was a secondary invader. Babes and Manolescu[2] also described a case in which in sections of the

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934.

heart vegetation, diphtheroid bacilli and in addition a few diplococci were found in an undulating layer on the outer surface of the fibrin layer. Howard[8] reported a case of a man of forty-four who had been sick for seventeen days with endocarditis but no clinical signs of diphtheria, from whom a bacillus morphologically a true Klebs-Loeffler bacillus, showing beaded forms and some clubbed ends were seen in sections and smears. Cultures on simple media were identical with true diphtheria bacilli. The organism failed to kill guinea pigs or rabbits. The bacteriology of this case was checked by Dr. Welch, but at that time no fermentation tests were done. This may possibly have been a diphtheroid organism. Herzog[7] also described a patient sick for four weeks who died of endocarditis without clinical signs of diphtheria. In the heart vegetations numerous diphtheria bacilli were found in smears and sections. Cultures from this killed a guinea pig in five days. No control animal given antitoxin was used.

Numerous reports are found in the literature concerning the mutation of organisms from diphtheroid to streptococcic forms. Mellon[11] and Rosenow[12] in this country have for a long time maintained that changes from the bacillary phase of an organism to the streptococcic phase can be produced by transferring the organism from solid media to proper liquid media. Jensen and Morton[9] described two strains, one derived from the urine of a case of cystitis and the other from the blood culture of a patient with subacute endocarditis, which they could change from diphtheroids on blood agar to streptococci in dextrose brain broth and back and forth at will. Sinek and Springer[13] described a typical case of subacute bacterial endocarditis in which a necropsy was performed; smears from the heart valve showed large numbers of streptococci. On culture a markedly hemolytic streptococcus was obtained but after repeated transfers it became similar to cultures obtained from the blood before death; it lost its power of hemolysis and both strains showed typical diphtheroid rods on solid blood-containing mediums and streptococcic chains in liquid mediums. Abercrombie and Scott[1] described a case of a boy of eighteen with congenital heart disease who died of sub-acute

bacterial endocarditis from whom Streptococcus mutans, which was non-hemolytic and non-green producing was cultured from the blood before death and from the heart vegetation at necropsy. This organism grew typically in chains of cocci on liquid medium but on glucose agar the majority of the organisms were typical diphtheroid bacilli. On changing to glucose-free medium the culture reverted to the original streptococcic form. These authors state that Clarke who described the organism first from carious teeth had observed three cases of fatal endocarditis caused by the same streptococcus.

Beck and Braun[3] described marked changes in the growth characteristics of various strains of streptococci and pneumococci when grown in urine, starting with mixtures of urine and broth and increasing the amount of urine. From all the various strains used, as the final product, enterococci (type B) were obtained, which resisted 60°C. for one hour and had lost their pathogenicity for animals. Fleck and Elster[6] also reported marked changes in colony structure and morphology in a pigmented strain of streptococcus by changing the medium or by sufficiently repeating transplants. Bacillary forms typical of Corynebacteria were obtained on solid media. Straus[14] in studying blood cultures from cases of chronic infectious arthritis obtained diphtheroids in seventy-four cases out of 750 cultures. By Mellon's method he was able to transmute twenty-four out of thirty-six of these cultures to streptococci, but he was unable to revert them back to bacillary forms. The bacillary forms varied from the streptococcic forms derived from them in their fermentation reactions and antigenic properties. Callow[4] found results similar to those of Straus in her extensive work. She cultured bloods from large numbers of cases of rheumatic fever, acute diseases of the respiratory tract, including tonsillitis and measles, miscellaneous febrile and afebrile diseases, and a series of normal persons. Of the rheumatic fever cases 70 per cent had a positive culture. Fifty-one per cent of the positive cultures were pleomorphic bacilli, 35 per cent were Streptococcus viridans, both organisms, 7 per cent, and 6 per cent were anhemolytic streptococci. In the series of acute respiratory diseases 70 per cent yielded a positive culture with

about the same proportion of the various organisms as in the rheumatic fever group. In the miscellaneous febrile group 6 per cent were positive, in the miscellaneous afebrile disease group 45 per cent, and in the normal person group 8 per cent. Most of the cultures from the afebrile cases and all the cultures from normal persons were pleomorphic bacilli. These grew with difficulty. Callow was able to transmute the pleomorphic bacilli into streptococci in all cases tried by culturing on potato phosphate broth. Some changed to anhemolytic streptococci, some to viridans type and a few to hemolytic strains. She concluded that "alpha diplostreptococci and pleomorphic bacilli may be recovered repeatedly from the blood of patients with rheumatic fever and certain diseases, mostly of the upper respiratory tract. These organisms apparently represent stages in the life cycle of the same organism. A specific etiological relationship between these organisms and rheumatic fever is questioned."

Thompson[15] in 1079 blood cultures taken in 730 cases of various illnesses at the Mayo Clinic, found 33 cultures of diphtheroids, an incidence of 3 per cent. Only one of the cultures, obtained from a case of subacute bacterial endocarditis, showed mutation to streptococcic forms when transplanted to liquid medium, and this form persisted on further subcultures. The others remained bacillary at all times. He concluded that diphtheroids appear to have the same significance in blood cultures as do saprophytic cocci.

These unique findings warrant special attention to pleomorphic or diphtheroid bacilli and even to streptococci when found in blood cultures. Only by repetition of similar experiments and thorough study of bacteria from cases examined post mortem, especially those of rheumatic and non-rheumatic cases, can the significance of these organisms be determined. The following case report deals with a case in which typical diphtheroid bacilli were found in blood cultures and in the heart valve. It could be mutated partly to streptococcic forms.

CASE REPORT

Mrs. A. H., housewife, age 36, had in her earlier years suffered from a variety of infections, including scarlet fever, influenza, typhoid fever at the age of fifteen,

and repeated attacks of tonsillitis. Her tonsils had been removed at the age of twenty-three. Nine years before her death she suffered an attack of acute rheumatic fever with mitral endocarditis, and had known since then that she had "leakage of the heart." Three years before death her upper teeth were extracted but there were left two roots which from X-ray evidence were not infected.

Eleven months before death she began to lose weight, fatigued easily and became nervous and irritable. In about three months she became bedridden because of increased weakness, slight fever, breathlessness and palpitation on exertion and slight diarrhea. Her attending physician, Dr. C. L. Haines, suspected a possible mild exacerbation of a minimal chronic pulmonary tuberculosis. Two months later she complained of rheumatic pains in her large joints. A blood culture at this time was reported as being negative. During the next two months her condition remained unchanged, and she was brought to the Pasadena Hospital on May 28, 1933 for study. She complained on admission of weakness, nervousness, loss of weight, palpitation, and pains in her shoulders and knees.

Physical examination revealed a moderately pale woman, fairly well nourished, showing no edema or pectechiae in the skin or elsewhere. The thyroid was negative. A moderate enlargement of the heart and a systolic and presystolic murmur was heard plainly at the apex and transmitted to the axilla, typical of a mitral stenosis. The spleen and liver were not palpable, no masses or tenderness were found in the abdomen. The rest of the examination was negative. Her temperature reached 100 to 101° every day, pulse 80 to 90, respiration normal.

Laboratory examinations revealed 11.3 grams of hemoglobin (Newcomer); erythrocytes, 3,510,000; leukocytes, 10,900; segmented neutrophiles, 35 per cent; non-segmented neutrophiles, 17 per cent; lymphocytes, 23 per cent; eosinophiles, 1 per cent; monocytes, 18 per cent, and histiocytes, 6 per cent. Many of the monocytes were immature and showed toxic budding. Many of the histiocytes showed phagocytosis of erythrocytes or nuclear fragments. The erythrocytes showed slight achromia and minimal variation in size. The urine was negative. Two blood cultures planted in infusion broth, brain dextrose (1 per cent) broth and pour infusion plates gave a pure growth of diphtheroid bacilli in all flasks and plates, averaging about 10 to 15 colonies per cc. of blood in the plates. (See below.)

A presumptive diagnosis of bacterial endocarditis was made and after a week she returned to her home. During the next two months her rheumatic pains continued, fever was constantly present, distressing attacks of paroxysmal tachycardia occurred at irregular intervals, associated with vomiting and diarrhea, which necessitated her second admission to the hospital on August 5, 1933.

By this time she had become markedly emaciated and anemic. The spleen was palpable three finger breadths below the ribs. The heart findings were the same as at first admission. A ballottable right kidney was palpable and in the

lower portion of Scarpa's triangle of the left thigh, deeper than the femoral artery, a hard tender, non-pulsating, fixed mass the size of a pigeon's egg was felt. About three weeks previously this mass had been exquisitely tender.

Laboratory studies at this time revealed 8.3 grams of hemoglobin (Newcomer); erythrocytes, 2,950,000; leukocytes, 9,700; segmented neutrophiles, 73 per cent; stab forms, 15 per cent; juveniles, 1 per cent; monocytes, 5 per cent; lymphocytes, 6 per cent. No histiocytes could be found. Several fresh urine

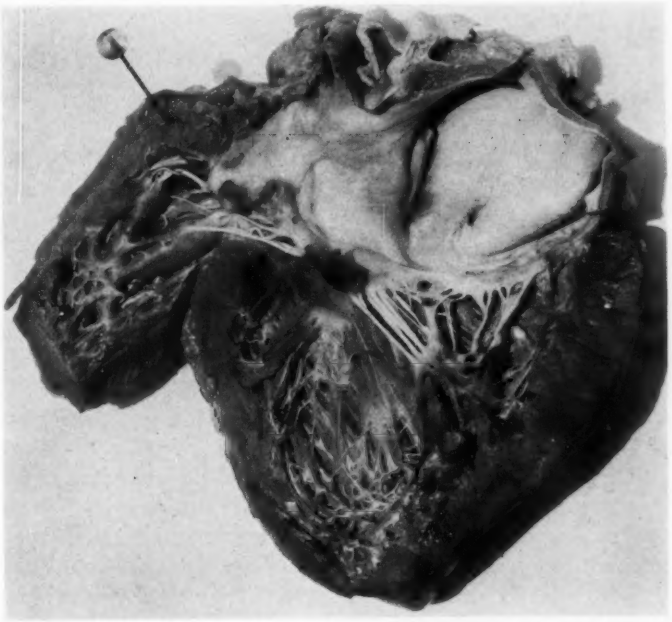

FIG. 1. HEART

Note the vegetations on the mitral valve and the old fibrous thickening of the leaflets and chordae tendinae.

samples were grossly bloody, showed 1+ to 3+ albumin, and a heavy sediment of leukocytes and erythrocytes. No casts were found. Smears and cultures revealed large numbers of hemolytic colon bacilli and streptococci but no diphtheroids. Two blood cultures gave a growth of diphtheroid bacilli similar to those cultured ten weeks previously.

The clinical course was steadily downhill until her death on September 12, 1933. During the last few weeks of life the urinary output decreased, the albumin content was always high, and erythrocytes were more numerous.

Terminally a few moderate sized ecchymotic spots appeared on the left forearm. She was anuric and comatose for the last few days. The final clinical diagnosis was made of subacute diphtheroid bacillus endocarditis, acute glomerulonephritis, acute pyelonephritis, uremia, and mycotic aneurysm of left thigh.

Necropsy was done two hours after death. The final anatomical diagnosis was: subacute recurrent diphtheroid bacillus endocarditis of mitral valve and old fibrous endocarditis of mitral valve with moderate stenosis and insufficiency; recent endocarditis of aortic leaflets; acute diffuse glomerulonephritis, uremic enterocolitis; acute right pyelonephritis and cystitis; completely thrombosed infective (mycotic) aneurysm of left profunda femoris artery; anemic infarcts of various ages in the spleen; marked anemia and emaciation.

The heart (fig. 1) weighed 230 grams (total body weight, about 36 kg.) and measured 11 cm. long and 9.5 cm. wide. The mitral leaflets showed considerable old fibrous thickening, in some places to 4 or 5 mm. thick, and fusion of the leaflets at the angles for about 1 cm. On the opposing margin of the anterior leaflet in its middle was found a bean-shaped vegetation, firm to the feel, measuring about 1.3 x 0.5 x 0.3 cm. and firmly fixed to the valve. The surface was fairly smooth, except at one end, which was somewhat roughened. On section there was marked organization at the point of attachment and an occasional fleck of calcium was found in the middle of the vegetation. Small, fine, firm, partly organized vegetations were found on the posterior leaflet, over its entire middle and extending onto the adjacent auricular endocardium, and at the angle between the two leaflets. There was moderate fibrous thickening, fusion, and some shortening of the chordae tendinae of both leaflets, chiefly the anterior.

A small, firm, gray vegetation 4 mm. across was present in the middle of the posterior leaflet of the aortic valve 5 mm. from its top margin. There was a moderate hypertrophy of the left auricular muscle. The muscle of the ventricles was pale and moderately soft. The coronaries showed no noteworthy changes. There were no congenital defects. The valves of the right side of the heart were normal.

Histological study of hematoxylin and eosin and Gram-Weigert stained sections through the vegetation and the deeper portions of the mitral leaflets (fig. 2) showed marked fibrosis and occasional small calcium deposits in the thickened part of the valve. Just external to this was a layer of granulation tissue showing many fibroblasts, round cells and macrophages, and on the surface the bulk of the vegetation was composed of partly hyalinized fibrin or necrotic material, in the meshes of which large colonies of bacilli were arranged in irregular masses or colonies, chiefly in the deeper layers. Some small colonies or groups of bacilli were found just at the margin of the granulation tissue and a few were found within macrophages. In Gram-Weigert stains the organisms were most plainly seen. They were strongly Gram-positive and were all bacillary in type, much longer on a whole than those obtained on cultures on blood agar, sometimes showing long filamentous forms, chiefly growing in colonies, but some were found

quite separate from these groups. No streptococci or other organisms were seen. Small masses of calcium were present in the necrotic portion of the vegetation. Large masses of poorly staining bacteria were commonly seen, and in some of these, calcium deposit was present.

The changes in the other organs are given sufficiently above. The infection of the pelvis of the right kidney and bladder was fairly recent as was the diffuse glomerulonephritis.

Cultures of the heart blood after death revealed a heavy growth of diphtheroid bacilli similar to those obtained in life. Cultures made aseptically from frag-

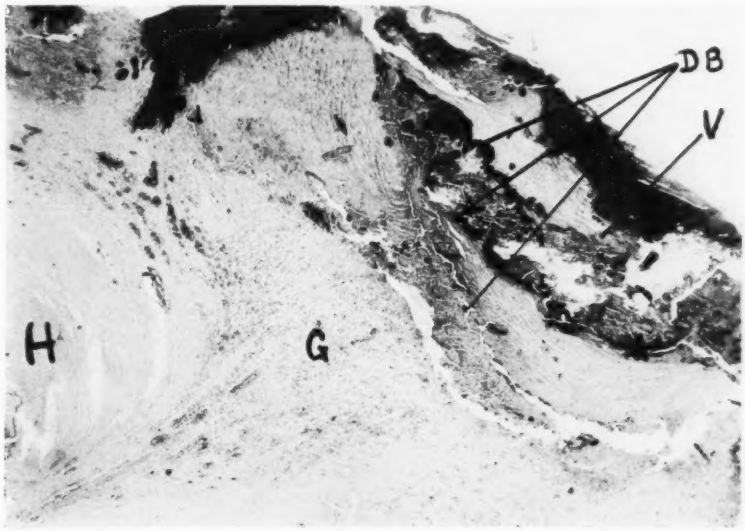

FIG. 2. SECTION THROUGH MITRAL VALVE

This shows masses of diphtheroid bacilli (D. B.) in the vegetation; hyaline fibrous portion (H.) and granulation tissue (G.) just below vegetation (V.).

ments of the heart vegetation yielded a heavy growth of the same organism. Smears of other pieces showed moderate numbers of Gram positive bacilli, chiefly elongated forms, separate or in clusters, of the same diameter as those found in blood agar cultures, but on the average about twice as long, and some long filaments as long as four or five average bacilli. No other organisms were present.

The organism in the original culture of the blood and heart valve in bouillon and blood agar grew slowly, and colonies in blood agar pour plates were about half the size of a pin head at their maximum growth, almond-shaped, and sur-

rounded by a narrow green zone. The surface colonies were round, gray, glistening, minute in size, and likewise showed a narrow green zone, but no hemolysis. The colonies were so much similar to green producing streptococci that we were always surprised on examining smears made from all the colonies that only

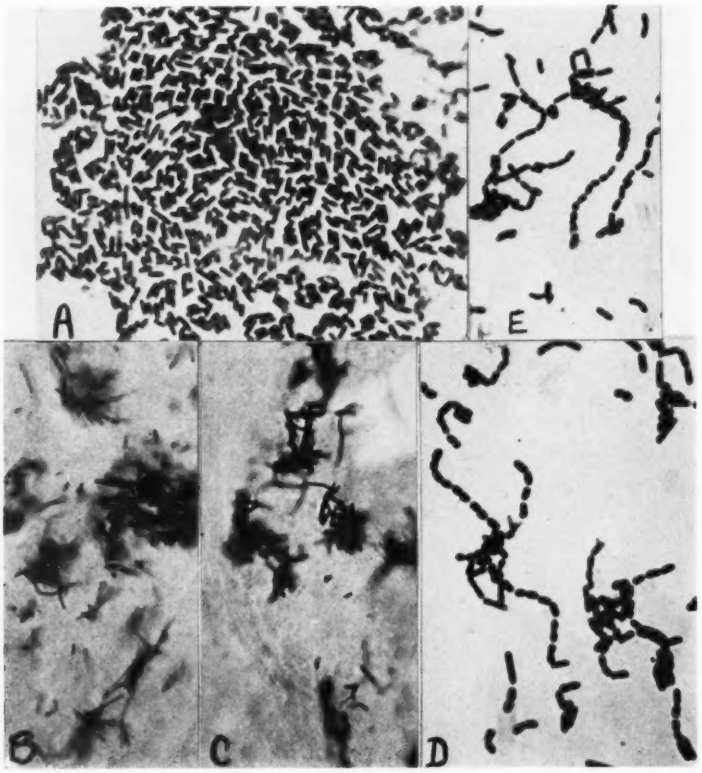

FIG. 3. MICROPHOTOGRAPHS OF BACTERIA

(a) Diphtheroids from the original blood agar cultures, (b) bacilli in a section of the vegetation of the mitral valve, (c) bacilli in a smear from the vegetation of the mitral valve and (d) and (e) streptococcic forms from plain broth.

bacilli were present. These organisms were typical diphtheroids showing palisade arrangement and no evidence of chain formation was present. They were straight, solid staining Gram positive rods of fairly uniform length with slightly rounded ends. On Loeffler's medium only solid staining forms were found. Original broth cultures showed organisms of similar character except that occa-

sionally they were arranged end to end, and on the whole were somewhat larger than those in the blood agar cultures, and occasionally filamentous forms like those seen in the sections of the heart valve were present. Smears of transplants made from single colonies of blood agar cultures into infusion broth, brain dextrose broth, and potato phosphate broth, as suggested by Callow, showed the organisms growing nearly exclusively in chains of bacillary forms, most of which resembled in size and shape the bacilli in blood agar cultures. Some long filaments were found and also some chains showed rounded forms indistinguishable from streptococci. Occasional chain showed part of the chain to be made of bacilli and parts to be streptococci in form. In some bacilli two densely staining ovoid or almost spherical forms could be seen, surrounded by an almost invisible, faintly staining residue of the original bacilli. Transplants made repeatedly over a period of eleven months revealed the same findings as seen on the first transplant. It has been impossible to produce a pure streptococcus from the culture on any medium by short or long periods of incubation. As soon as the organism was transplanted back to blood agar, only long rods were produced and no streptococcic forms were seen. Some chains of bacilli were present, but palisade arrangement was chiefly produced. A culture made for us by Dr. Ralph Mellon from a single bacillus showed the same morphological and cultural characteristics as those of the cultures made by picking isolated colonies from the heart valve and blood cultures.

The organisms in broth culture produced acid and no gas in glucose, maltose, saccharose, salicin, but produced no change in mannite, inulin, levulose, raffinose and lactose. It produced no indol. Growth on human serum agar containing 1 per cent sugar showed identical fermentation reactions with glucose, lactose, saccharose, maltose and mannite, the only sugars planted.

The blood serum of the patient agglutinated the organism in broth cultures at a dilution of 1:5120, and a strain of Streptococcus viridans from root abscess of a tooth of another patient, in the same dilution. Serum from a normal person failed to agglutinate either of these organisms at 1:20 or higher dilutions. Several times animals were injected intravenously with large amounts of broth cultures with no untoward results. On one occasion the growth from six blood agar slants was washed off in a total of 8 cc. of salt solution. Intravenous injection of 1.5 cc. of this was made into a white mouse, 3 cc. into a rabbit, and 2 cc. given intracardially to a guinea pig and 1.5 cc. into a rat, intraperitoneally. All the animals showed no effects from the injection. Subcutaneous injection of larger amounts into white mice and a guinea pig likewise produced no infection.

SUMMARY AND CONCLUSIONS

A case of subacute bacterial endocarditis running a typical clinical course and showing typical post mortem findings is presented. From the blood on four occasions during life and from

the blood and heart valve after death a diphtheroid bacillus was recovered in pure culture. Smears and sections of the heart valve revealed large numbers of the same organism with no other organism present. The serum of the patient obtained after death agglutinated the organism in high dilution. On liquid media streptococcic forms were produced, but only bacillary forms were found on blood agar.

This case well demonstrates that diphtheroid bacilli in blood culture may be of vital importance and are not always simple contaminants. The entire clinical and pathological picture presented by this patient and the bacteriological studies point strongly to the view that the organism obtained is only a stage in the life cycle of a green producing streptococcus. It is recommended that all strains of diphtheroid bacilli obtained from human cases of infection be cultured on appropriate mediums in order to demonstrate their relation to streptococci.

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EDITORIAL

Tuberculin P. P. D. (Purified Protein Derivative)

In 1890, the world was advised of a new discovery by Robert Koch, the patient, painstaking bacteriologist. The new product, a preparation from tubercle bacilli, at first advocated for therapeutic purposes, was finally, in the early 20th century, established as a reliable diagnostic agent in tuberculosis by von Pirquet, Calmette, Mantoux, and others, for both animal and man. Its value as a diagnostic agent and especially for intelligent survey purposes in man is undenied at present.[1] In veterinary practice, it is now even more extensively used than in human practice. To the genius of Robert Koch must be credited the recognition of the protein nature of the active principle of tuberculin, although the tests used by him might be considered rather crude today and leave a suspicion of doubt because the pure active principle had not been prepared by him; yet his experiments can be repeated with identical results. Tuberculin O. T. (old tuberculin Koch), the original glycerol broth concentrate upon which tubercle bacilli had been grown, defied the best chemical efforts for obtaining the pure active principle and it remained for Long[3] to initiate studies in 1919 for preparing a non-protein synthetic medium suited for growing tubercle bacilli with which the problem could be studied chemically, and finally for Seibert[5] in 1928 to prepare the active principle in crystalline form. To the chemist, the preparation of crystals assured chemical purity, and so tuberculin was proved to be a pure crystallizable substance of protein nature. At the same time Seibert[6] devised a method for preparing a standard undenatured tuberculin of any desired strength and presented a method of chemical assay, which made for more exact chemical production and disposed of elaborate and extensive biological testing as a guarantee of uniformity. Then arose the practical question of the advantages, if any, of

the chemically pure tuberculin as compared with the time-honored O. T. so universally used and accepted by the medical and veterinary professions. Tuberculin T. P. T.[7] (meaning tuberculin, protein precipitated by trichloracetic acid) solutions were found to be relatively stable and stock solutions of any strength, equal to or greater than that of O. T., could be prepared. Preliminary clinical tests indicated that 0.0001 milligram or less of T. P. T. will produce a skin reaction in tuberculous patients, and it is a safe and satisfactory product for diagnostic purposes. Human tests with the pure tuberculoprotein have been variously carried out, and, because of slight modification in preparation by the different commercial firms coöperating in this endeavor, the tuberculoprotein has been given different names. Thus, "M A 100" is one designation used in the Johnson chart for chemical analysis of the tubercle bacillus according to numbers assigned to Mulford and Company. Mariette and Fenger[4] conclude that M A 100 human protein is as sensitive and as selective as O. T., and probably more so, and the initial and repeat doses are safe and large enough to pick out the majority of tuberculous individuals. They believe it a better testing substance than O. T. because of its purity and the ability to weigh it accurately. Lichtenstein[2] used T. P. T. obtained from Seibert on 944 tuberculous adults and found 97.7 per cent reacted to a diagnostic injection of 1:1,000 dilution, starting with a 1:1 dilution consisting of 10 mgm. per cubic centimeter, which is equivalent to undiluted O. T. (Parke, Davis & Co.). He believes it a reliable form of tuberculin for intracutaneous testing, and found skin sensitivity to diminish as the lesion becomes more extensive, as the symptoms become more intense, and with duration of the disease. More recently, the commercial product has appeared as P. P. D. (purified protein derivative) (Parke, Davis & Co. and Sharp and Dohme) in tablet form in milk sugar. The tablets are available in two strengths, for the first test 0.0002 mg. and for the second 0.05 mgm., which is dissolved in 1 cc. of buffer diluent supplied with the tablets, thus assuring the use of fresh solutions of the pure substance responsible for the specific reaction. Although it is only contended that the pure substance is as sensi-

tive and as selective as O. T. by those who have clinically compared the materials, it must be admitted that the presence of minute amounts of extraneous protein in O. T. should recommend the use of the pure tuberculoprotein for diagnostic purposes. Its therapeutic use has not been stressed commercially, or in scientific publications, up to the present; and although there appears to be no obvious obstacles to the therapeutic use of the pure tuberculoprotein, it may be well to await further studies and instructions before proceeding in the case where small differences may mean profound effects, especially in such a place as the eye.

—H. J. CORPER.

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NEWS AND NOTICES

Minutes of 1934 Meeting of American Society of Clinical Pathologists in Cleveland, Ohio

The business meeting was called to order by President Foord on Sunday evening, June 10th at seven o'clock in the Empire Room of the Hotel Cleveland. The minutes of the previous meeting were approved as published in the official Journal. Reports of Committees followed.

REPORT OF SECRETARY-TREASURER

As indicated in the circular communications sent out to the membership your officers have devoted a great deal of thought to questions of economic and scientific aspects. Some of these questions will be presented to you for discussion by various Committees. I wish to call to your attention particularly a problem which needs to be solved and that is the pernicious practice of hospitals in the field of clinical pathology. During the past year the radiologists and anesthetists have brought this problem to the attention of the American Medical Association and various States. In some States the problem has already been solved under the medical practice act, such as in California and Indiana. The Attorney-Generals have ruled that anesthesia should be given by physicians and not by laymen. The Council on Radiology has prepared a resolution which will also be read at this meeting and which so far has received the endorsement of the American Medical Association.

Your Secretary is very glad to report that the membership has responded nobly in paying dues as by June first 321 members had paid their dues in full out of a total of 390. Two members have been dropped for non-payment of dues, three have resigned and four have died. The appended financial report reveals that the Society still has been able to operate without cutting into the surplus. Please note that the income exceeds the expenditures by only $859.00 and $520.00 of this represents application fees, some of which may have to be returned. Further, that the membership receives in the Journal 63 per cent of their ten dollars. It is obvious that we are operating on a very close budget.

Your Secretary is very grateful to the membership for the coöperation accorded him particularly by the various Committees and officers of the Society.

A. S. Giordano, *Secretary-Treasurer.*

Motion made and seconded for acceptance of report. Carried.

FINANCIAL REPORT OF SECRETARY-TREASURER

Assets

Balance on Deposit—City National Bank			$2,625.97
Investments:			
Commonwealth Edison Company #41022 4 per cent First Mtge. Gold Bond Series F-1981	$1,000.00	$945.00	
American Telephone & Telegraph Co. #70378 5 per cent Coll. Trust Gold Bond 1946	1,000.00	1,025.00	
City National Bank, Cert. #8 28 Shares Common Capital Stock	280.00	336.00	2,306.00
Furniture and Fixtures		$601.75	
Reserve for Depreciation		601.75	
Balance on Deposit—Citz. National Bank in Liquidation by Receiver			655.38
Total assets			$5,587.35

Motion made and seconded for acceptance of report. Carried.

REPORT OF BOARD OF REGISTRY

In our annual report for the year from May 1, 1933 to April 30, 1934 inclusive, we are gratified to record a continuation of the good progress of the Registry of Technicians. For the first time in our brief history, applicants were required to take an examination before being granted a certificate of qualification. These tests which are held semi-annually were conducted simultaneously in various cities of the United States and Canada, the first in October 1933 and the second in April 1934. They consisted of a practical and a written part, the questions having been prepared by a member of our Board.

At the October examinations sixty-seven applicants participated, of which number, fifty-six passed successfully. In the April tests there were 128 candidates. The results are not available at the time this report is written. At the first national examination we had thirty examiners, while during the recent one, forty-nine took part. We take the opportunity here to express our thanks to the colleagues who have given freely of their time and labor in furtherance of our cause to raise the status of the laboratory technician. Their services were entirely gratuitous, often at a personal sacrifice and carried out the traditional spirit of our profession in the interest of humanity.

During the past year, 288 registrants were added to our rolls, of which 251 received the designation of Laboratory Technician and thirty-seven were awarded the appellation of Medical Technologist. The total number of registrants at the end of our fiscal year is 2237, comprising a large fraction of the best technicians in the United States and Canada.

As in the previous years, we have been greatly assisted in this work by the hearty endorsement and coöperation of the American Medical Association, the American College of Surgeons and the American Hospital Association.

During the past year the work of the Registry was made known to wider circles of the medical profession and hospital administrations by interesting graphic exhibits held at the National conventions of the American College of Surgeons at Chicago, the Southern Medical Association at Richmond, Virginia, and the American Hospital Association at Milwaukee. These exhibits were designed and personally supervised by Dr. Roy R. Kracke, a member of our Board who was aided in the respective localities by Fellows of the American Society of Clinical Pathologists.

A major concern of the Registry is the supervision of training of technicians. It has been the endeavor of the Board to bring the teaching progressively up to the highest level commensurate with sound knowledge and efficiency of the students. To this end certain standards have been set up which have been gradually elevated from year to year as experience dictated. We do not approve any schools organized for profit and are encouraging the affiliation of training schools with universities and colleges of learning, always of course, under the direction of a competent clinical pathologist. At present students must have had a year's course in college chemistry and biology prior to entering training. A model curriculum for training schools has been set up by Dr. Asher Yaguda and is now awaiting approval and amendments by the Board prior to publication.

A very gratifying feature of the supervision of training schools is the valuable help and coöperation accorded us by the Council of Medical Education and Hospitals of the American Medical Association. Dr. William D. Cutter, the Secretary, has been conferring with our Board and has generously lent us the services of the Council's field men to inspect training schools in the course of their periodical inspection of hospitals for the American Medical Association.

The finances of the Registry, we are happy to state, are in a satisfactory condition due to the economy practiced and the fact that the members consider it a privilege to serve without compensation in this altruistic function of our Society. To insure safety of our funds all reserve above current expenses has been invested in Government Bonds and both principal and interest are held in trust by a trust company subject to the disposition of the lawful chairman and two members of the Board membership. A detailed financial report with audit by a certified public accountant has been transmitted to the Executive Committee. A summary of the financial report is herewith appended.

The office work of the Registry has grown to enormous dimensions, involving a vast correspondence with registrants, applicants, clinical pathologists, physicians, hospitals and seekers for information. It has necessitated additional equipment and hiring of extra help.

The complexity and organization of the Registry office is now in such a state of development that continuity is highly desirable and a change to another location would be fraught with difficulties.

The Board desires to express its appreciation of the valiant and efficient work done by the Registrar, Mrs. Anna Ruth Scott, who has endeared herself to all the registrants and to the members of the Board by the painstaking and tactful management of her arduous duties.

We thank the Fellows of our Society for their helpful coöperation with our Registry.

PHILIP HILLKOWITZ, *Chairman.*

FINANCIAL REPORT

Balance in Bank, May 1, 1934	$5,208.50
Total Income, May 1, 1933 to April 30, 1934	5,185.72
Total	$10,394.22
Disbursements, May 1, 1933 to April 30, 1934	8,095.28*
Balance	$2,298.94

* Includes purchase of $3,000.00 U. S. Government Bonds.

Motion made and seconded for acceptance of report. Carried.

REPORT OF COMMITTEE ON PUBLIC RELATIONS

The work of your Committee on Public Relations for the past year has been of two kinds, clerical and deliberative.

The clerical work has consisted of the compiling of information submitted by the Society's Counselors. We have prepared a list of physicians in the United States who are making tissue diagnoses and from it we can ascertain the distribution of this service. Maps showing this distribution have been prepared to furnish visual aid in the study of the situation. We also have information from twenty States as to the legal relation of clinical laboratories to the practice of medicine. This in most cases consists of the opinion of an attorney concerning the effect of the State's Medical Practice Act.

Our list of tissue pathologists includes more than 860 physicians who are reported by the Counselors of the American Society of Clinical Pathologists to be making diagnoses of tissue. Some of the State lists include only those who are doing laboratory practice exclusively, while others also include internists or surgeons who undertake tissue diagnosis in connection with their clinical work. No concerted attempt has been made to gauge the ability or experience of the individuals listed.

In accord with the spirit of the times, we must consider the question of certification of tissue pathologists. Opinions differ concerning how this should be done, or whether it should be done. No method will be entirely satisfactory. One essential thing is to encourage adequate early training and frequent postgraduate study. The latter is indispensable for those whose routine material is limited in amount.

There should be general acceptance of the principle that the small hospital, unable to provide for a competent pathologist in attendance, should obtain such services elsewhere, preferably from the most competent, readily-available pathologist. Certification of some sort will help locate the competent diagnosticians. The personality of the pathologist, and the ability or willingness of the hospital to pay for competent service, must combine to produce the final solution of the problem.

One of our members, writing about his problems, has said, "The most crying need is for the education of the profession in how to use the pathologist and the laboratory to the greatest benefit of themselves and their patients." To this end, pathologists should appear on State and County Society programs frequently. Whether the appearance is before one's own society, or in a neighboring one, it is perhaps better to discuss common things, rather than only rare cases.

During the past year editorial writers and others have questioned the presence of a demand for our specialty, implying that its most profitable use is as a means of preparing for and entering clinical practice. Such a belief may be fostered by the excellence of training in the laboratory sciences which is offered as part of the present day medical curriculum. The new medical graduate feels that he is already competent in the laboratory and needs only experience to become a clinician. Certainly some of today's clinical pathologists will be clinicians tomorrow. Perhaps it is heresy to acknowledge this, but it would be worse heresy to encourage it. So long as such a situation continues, the incorrigible clinical pathologist can be accused of deficiency either in ambition or in ability. His only defense is to progress medically so far beyond the casual laboratory worker that confusion can no longer exist.

Reports of Counselors concerning State regulations about laboratories conducted by lay technicians have been much alike. Some Medical Practice Acts were written before the clinical laboratory was a factor in the care of the sick. More recent laws include "diagnosis" as part of the practice of medicine, but it remains a question whether the report of a laboratory procedure is diagnostic until interpreted. Such interpretation to the laity by a lay technician has been held to be the practice of medicine. A legal opinion in one State holds that it is not improper for the technician to interpret his findings to a physician. The Council on Medical Education and Hospitals of the American Medical Association has coöperated with our Society since 1923 in emphasizing the need of skilled medical interpretation of laboratory findings. If it is desirable to make this legally compulsory, we must continue to work with and through the American Medical Association and its component societies. We should have a more or less permanent committee to consider with the American Medical Association all matters involving our common welfare, or in which the support of the entire organized profession is essential.

The question has already arisen as to whether a hospital has the right to employ a pathologist on a fixed salary and make charges to patients for his services. This common practice is apparently illegal in some States and under attack in others. If the disturbance becomes general, some hospitals will inevitably solve the problem by ceasing to employ pathologists. Others will join the ranks of those small or poorly financed institutions which are now using members of their clinical staffs as laboratory supervisors without salary. As an economy measure this may perhaps be better than the employing of an unsupervised technician. The tendency for such supervision to become purely nominal, however, makes the practice a questionable one on which to base the approval of a hospital-grading body.

It does not seem unreasonable to hope that every approved hospital of 50 beds or more will sometime be required to have a competent clinical pathologist in charge of its laboratory. The size and type of service will determine how much of the pathologist's time is needed.

In general the pathologist has come to consider an adequate salary a satisfactory method of compensation. If this arrangement is found to be contrary to law, or at variance with public and professional welfare, it may be possible for the pathologist to rent from the hospital its laboratory facilities and conduct them as a private diagnostic service.

The hospital roentgenologists have a somewhat similar problem and the American College of Radiology has recently (February 13, 1934) passed resolutions looking toward a remedy. There is appended to this report a somewhat similar set of resolutions, for the consideration of the Society at this meeting.

We cannot and should not get away from the consideration of the economic problems which are peculiar to the practice of clinical pathology. New ones will come and go and the Society's influence will help solve some of them.

Right now there is a well-publicized sentiment against specialization in medicine. Excessive expense for non-essential service is claimed. It is inevitable for the true clinical pathologist to believe that modern medical science and practice needs and will continue to need his services.

The most urgent suggestions presented this year by the Society's Counselors have been these—

First, know more about laboratory measures and their use than do the clinicians who may call for your help, and

Second, figure out some way to make your skill available to and desired by your clinical associates.

The following resolution is presented in accordance with the recommendation and vote at the Round Table meeting, Friday, June 8th, 1934.

Whereas, it has come to the attention of the American Society of Clinical pathologists that certain practices are now in operation in many localities, adversely affecting the practice of clinical pathology and the best interest of the patient, and

Whereas, The American Society of Clinical Pathologists wishes to support the

resolutions of the American College of Radiology made under date of February 13, 1934 that it is the function of the physician to furnish medical care and of the hospital to furnish hospitalization, and

Whereas, Clinical Pathology is a medical specialty, comprehended in the practice of medicine and recognized by the American Medical Association, and

Whereas, The principle is recognized by the American Hospital Association, the American Medical Association and other national medical organizations that hospitals and other corporations or lay groups should not enter into the practice of medicine.

Therefore, Be it resolved by the American Society of Clinical Pathologists that all such practices are hereby condemned as prejudicial to the interests of both the medical profession and the laity, and contrary to sound public policy, and

Be it further resolved, That a copy of these resolutions be sent to the Council on Medical Education and Hospitals and to the Bureau of Economics of the American Medical Association, to the American Hospital Association, to the American College of Surgeons and to any other organizations as the Executive Committee may direct, requesting the support of the above named organizations in combating such practices.

C. W. MAYNARD, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

REPORT OF SEROLOGIC CONFERENCE COMMITTEE

The desire of conducting a North American Conference on serologic methods in the diagnosis of syphilis similar to those conducted by the League of Nations has been constantly in the minds of certain members of the Society. During Dr. Simpson's year as President, he personally stimulated a great deal of interest in the subject and his preliminary investigations on ways and means are in the hands of the present Committee. Immediately after becoming President, Dr. Foord asked me to form a Committee to investigate further the feasibility of such a Conference to be sponsored and conducted by the American Society of Clinical Pathologists. Dr. Simpson was asked to serve on this Committee. Following an appeal to Surgeon-General Cummings of the United States Public Health Service, Dr. Vonderlehr, appointed for special work in venereal disease control, became most actively interested in the project. His constant thought and efforts have been most valuable in outlining a specific plan for carrying out such a Conference.

His plan calls for the collection by the United States Public Health Service of 500 blood serum samples from known syphilitics, treated (400) and untreated (100), 500 serum samples from probable non-syphilitics, 100 serum specimens from lepers at Carville, Louisiana, 300 whole blood samples (serum not removed)

and, if possible, 150 cerebrospinal fluid samples. All of these to be partitioned and distributed as quickly as possible (by air mail to distant laboratories) to certain selected representative serologists who have developed individual methods. These to be tested by these serologists by their own methods in their own laboratories. After distribution of all samples, two months should serve as the time for collecting data from the serologists. Following this there would be a meeting in Washington, D. C. of the committee of five, two representatives of the Society, two recognized syphilologists and a United States Public Health officer to evaluate the data and make recommendations. Formal announcement of the results to be made at the regular meeting of the American Society of Clinical Pathologists and the release of the material in printed form by the United States Public Health Service.

The Committee has approved of the plan. An application for grant-in-aid was made to the National Research Council on March 10, 1934 for the sum of approximately $3,000, the amount necessary to carry out such a Conference in addition to the very valuable aid amounting to nearly $5,000 to be furnished by the United States Public Health Service. On May 23, 1934 this body announced its regrets at being unable to grant the request.

However, because of the continued interest of the Surgeon-General, Dr. Vonderlehr and other officers of the United States Public Health Service, I recommend that the Executive Committee approve in principle of the plan outlined, and that a Committee be granted power to continue to represent the Society and to carry out such a Conference if it seems possible to do so.

A. H. Sanford, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

REPORT OF COMMITTEE ON INVESTIGATION OF MOLDS

In response to a motion passed at the Milwaukee meeting of 1933, Dr. A. G. Foord has appointed an additional standing Committee on the Investigation of Molds. This Committee was requested to establish some scientific connection whereby any members could submit cultures for identification, and further to establish criteria for diagnosis of the ordinary fungus infections met with by the practicing clinical pathologist.

During the past year your Committee has investigated the field of fungus infection to the extent that it is apparent that it is impossible to have anyone to identify a given culture of any fungus that would establish proof of pathogenicity.

We have decided that a collection of findings proving growth and reproduction of pathogenic fungi can only be established by a collection by members of sufficient data to establish such criteria and the publication by this Society of such a collected study as a standard method of diganosis of fungus diseases.

At present we can only present a report of progress and request the continued support of the Society in the collection of material for study.

F. M. JOHNS, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

REPORT OF NECROPSY COMMITTEE

The Secretary of the Society sent out a questionnaire to the membership of the Society asking for data concerning the number of deaths, the number of postmortems and the situation in each locality concerning the obtaining of autopsies. To this questionnaire the Committee received ninety-six replies from pathologists and institutions. These have been tabulated according to States and some very interesting statistics and information has been obtained.

It is hoped that the activities of the Committee will be continued not only with the Society's membership but perhaps by securing coöperation with the American Hospital Association's Committee on Postmortems. By interesting that Society's membership we may be able to secure more complete statistics and secure information concerning many local situations, etc. At some future time then the Committee could publish the information, showing methods of coöperation between hospitals, doctors, undertakers, coroners, etc., that should be employed in order to improve the postmortem situation throughout the United States.

A. V. ST. GEORGE, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

REPORT OF THE TUMOR REGISTRY COMMITTEE

Being the only member of this Committee attending the Annual meeting, this report is essentially a personal communication.

The Tumor Registry is attempting to collect rare, interesting and border-line cases for the ultimate purpose of loaning these slides in groups to members of the Society. In another year this loan feature should be in operation. I recommend that the Tumor Registry Committee attempt to arrange a scientific exhibit at the next annual meeting of this Society.

The Registry is, and will be for sometime, in an experimental stage. Many local slide registries are springing up and to these some of the members are doubtlessly contributing. One of the older, larger and well-known registries has been discontinued during the past year because of lack of funds. So far the expense of this Registry has been negligible. It has been somewhat of a disappointment to find that some of the larger institutions are either unwilling or officially opposed to registering cases. It is apparent that there are several obstacles in the path of the success of this Registry which can be overcome only by the interest, support and enthusiasm of the members.

One important obstacle is the geographic separation of the members of the Committee. The Registry has two important duties as soon as a case is received. The first is to make a final and definite classification of the purpose of filing and the second is to correspond with the sender informing him of the opinion of the Committee and the diagnosis under which the case is filed. A third might be added, which will become continually more important, and that is to follow each case until death or for several years. It is generally admitted that the pathologist should know more about the prognosis of malignant diseases and additional information of this nature can only be acquired through an efficient "follow-up" system. The consultation and diagnostic service which this Committee renders is of the utmost importance for its ultimate success. The majority of the cases submitted to any registry are sent in for an opinion. This feature of the Registry has been lax and correspondence has been delinquent. Reasons for this, I believe, are obvious. One suggestion to overcome this obstacle would be to substitute for the Committee, a director who is a tissue pathologist of international repute whose opinion would not be questioned. Such a man would probably not have sufficient time to devote. A more practical suggestion would be to appoint as a committee the members of the Society in one city or one comparatively small area. Such a group could meet once a week and discuss intimately any cases received. In this way an efficient consultation service could be maintained which I am convinced is most important. Such a registry should be allowed to remain in one locality for at least two or preferably three years and then change to another city or area. While it is in one locality it certainly should absorb the desirable material in that locality for several years back. I earnestly recommend to the President and Executive Committee that the Tumor Registry Committee in the future be so appointed.

I believe the Registry Committee must be aggressive and must contact the men who, by personal contact or through their publications are known to have desirable cases for registration. Most of those I have received to date have been the result of personal correspondence. More explicit directions for sending the material to the Registry will be mailed to all members in the near future.

OSBORNE A. BRINES, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

REPORT OF NECROLOGY COMMITTEE

It is with a spirit of humility and sadness that the Necrology Committee submits the following report. During the last year four of our members have died.

Obituaries

Marian E. Parker died in Kalamazoo, Michigan, September 8, 1933 of pulmonary tuberculosis and poliomyelitis. She was born on April 4th, 1895 in New York; graduated from Syracuse University Medical School in 1926; was a

member of the Staff of Maybury Sanatorium at Northville, Michigan and in 1929 located in Kalamazoo where she practiced until her death.

O. J. West passed away in Seattle, Washington, September 17, 1933. A native of Oregon, where he was born in 1866, he graduated from the Willamette Medical School of Portland, Oregon in 1888. In 1900 he commenced pathology with Dr. Robert Zeit of Chicago in the Chicago Post Graduate School where he remained for almost ten years. Then he again answered the call of home and the West opening the first clinical laboratory in Seattle in 1910. Here he also served as director to several hospital laboratories including the Providence, and was pathologist to the Harborview Hospital for the last two years. His recreations were hunting, fishing, golfing and teaching.

April 5th, 1934, **J. H. Litterer,** age 41, died of heart disease in Nashville, Tennessee. Born in Nashville he successfully pursued his education in his home town, obtaining a Phi Beta Kappa key from the College of Arts and Sciences and a medical degree from the School of Medicine of Vanderbilt University. During the World War he served as a Captain in the U. S. Medical Corps.

Ohio State University was shocked on the morning of March 5th to learn of the sudden death from coronary thrombosis of **Ernest Scott** who the week before had successfully managed the College of Medicine Centennial. A native of the State of Ohio being born in Athens, Ohio in 1875 and closely connected with the University since his father is the only living former president, he graduated from Ohio Medical University in 1900. He taught at his Alma Mater and at Sterling-Ohio Medical College, joining the Ohio State faculty in 1910 where he was chairman of the Pathology Department and secretary of the college.

It is fitting that we stand a moment in bowed meditation in memory of those comrades who have preceded us to the Land of Everlasting Peace.

There are many heroes who live and die
Of whom we have never heard,
For this great big brawling world goes by
With hardly a look or word.

But one of the bravest and best of all
Of whom the list can boast,
Is the man who falls on duty's call,
The man who dies at his post.

He who battles disease when death draws near,
And faces his fate each day,
Yet strives to help and comfort and cheer
His comrades along the way.

Who goes his way while he yet may do
And smiles when he suffers most,
It seems to me is a hero true,
The man who dies at his post.

J. J. Moore, *Chairman.*

Motion made and seconded for acceptance of report. Carried.

NEW BUSINESS

Motion made and seconded to accept the resolutions made by Dr. Maynard in his Public Relations Committee report. Carried.

The following resolution made by Dr. Hunter was accepted:

a. That a Committee be appointed to investigate the feasibility and practicability of establishing life-memberships in the American Society of Clinical Pathologists.

b. That the Committee investigate the practicability of the establishment of a fund for the purposes of promoting the interests of the American Society of Clinical Pathologists in particular and Clinical Pathology in general. Contributions to this fund may be made by members of the Society by direct cash payments, insurance policies taken out in favor of the Society, or as may be left to the Society by wills from the estates of deceased members.

c. That the Committee bring in a report and recommendations concerning the establishment of life-membership and the special fund for consideration by the Executive Committee and the American Society of Clinical Pathologists at the next annual meeting.

Motion made by Dr. Rhamy that a liaison committee, carefully selected, be appointed to coöperate with the American Medical Association and other agencies on economic questions and to establish by law and otherwise that clinical pathology is a definite specialty of medicine, to the end that the practice of this branch of medicine by laymen and by corporate or lay institutions or organizations be controlled or prevented. Passed.

Resolution made by Dr. Rhamy that a special Committee be appointed to study and devise ways and means by which a registry for the certification of tissue pathologists could be established by the Society. Passed.

Motion made by Dr. Exton that the President appoint a Committee of as many as he deems fit to consider from every point of view the practicability of the Society publishing a work on Clinical Pathology. This Committee shall report their conclusions to the President and Executive Committee, who if they think the project advisable are hereby empowered to appoint the Editor and Subeditors in the various specialties, and make any necessary financial arrangements that will enable the preparation of the material to go forward without waiting for the next meeting of the Society. Passed.

Revision of Constitution and By-Laws

As adopted at the meeting of the American Society of Clinical Pathologists, Cleveland, Ohio, June 10, 1934

CONSTITUTION

Article I—Name

This organization shall be known as the American Society of Clinical Pathologists.

Article II—Objects

The objects of this Society shall be: (a) To promote the practice of scientific medicine by a wider application of clinical laboratory methods to the diagnosis of disease; (b) to stimulate original research in all branches of clinical laboratory work; (c) to establish from time to time standards for the performance of various laboratory examinations; (d) to elevate the scientific and professional status of those specializing in this branch of medicine; (e) to encourage a closer coöperation between the practitioner and the clinical pathologist.

Article III—Membership

Section 1. The membership of this Society shall consist of (a) Fellows, (b) Associate, (c) Honorary, and (d) Corresponding Members.

Sec. 2. Fellows shall be graduates from recognized medical schools who have specialized in the practice or teaching of clinical pathology (the latter to be in a recognized medical school) for at least three years after graduation and who are devoting a major part of their time to this field. They shall be members in good standing of their county and/or state medical society and of the American Medical Association. For the purposes of this section Clinical Pathology shall be defined as that branch of the science and practice of medicine which consists of the application of pathologic anatomy, physiology, chemistry, parasitology and bacteriology to the diagnosis of disease.

Sec. 3. Associate members shall be graduates of recognized scientific institutions who have made such contributions to any of the sciences relating to clinical pathology and whose membership will so further the objects of the Society as to make them eligible for associate membership. Associate members shall pay the regular dues and have all the privileges of Fellows except those of voting and holding office.

Sec. 4. Honorary members shall have distinguished themselves by research or personal sacrifice in the cause of scientific medicine to warrant their recommendation for election by the Board of Censors. They shall have all the privileges of active members except those of voting and holding office. They shall be exempt from paying dues.

Sec. 5. Corresponding members shall be residents of foreign countries in

good ethical standing who have distinguished themselves in any of the branches of clinical pathology. They shall be exempt from paying dues.

Article IV—Officers, Members of Standing Committees and Terms of Service

SECTION 1. The officers of the Society shall consist of a President, a Vice-President, a President-Elect and a Secretary-Treasurer. The President and Vice-President shall serve for one year. The President-Elect shall enter upon the duties of President at the annual meeting following his election. The Secretary-Treasurer shall serve for three years.

SEC. 2. The Standing Committees of the Society shall be an Executive Committee; a Board of Censors and a Board of Registry of Technicians.

SEC. 3. Officers and members of Standing Committees are to be proposed by the Nominating Committee or nominated from the floor by a Fellow of the Society and shall be elected by a majority of the votes cast at the annual business session.

SEC. 4. The Executive Committee shall be composed of six Fellows of the Society who shall each hold office for three years or until their successors are elected, two to be elected annually.

SEC. 5. The Board of Censors shall be composed of six Fellows of the Society who shall each hold office for three years or until their successors are elected, two to be elected annually.

SEC. 6. The Board of Registry of Technicians shall be composed of six Fellows who shall each hold office for three years or until their successors are elected, two of them to be elected annually.

SEC. 7. Officers and members of Standing Committees shall transfer promptly to their successors all funds, books, manuscripts, vouchers and other property of the Society on termination of their offices.

Article V—Meeting Place

The time and place of the annual meeting and other meetings of the Society shall be determined by the Executive Committee, notice of which shall be mailed to every Fellow at least thirty days prior to such meeting.

Article VI—Quorum

Twenty-five Fellows shall constitute a quorum.

Article VII—Amendments

This Constitution may be altered or amended by a vote of three-fourths of the Fellows voting at a regular meeting in executive session, provided said alteration or amendment had been submitted to the membership by publication or otherwise at least thirty days prior to the annual meeting.

BY-LAWS

Article I—Applications for Membership

Application for membership shall be made on a form authorized by the Society, signed by the applicant, recommended by two members and approved by the local Counselor and the Board of Censors. At least thirty days prior to the convention the Secretary shall send a list of applicants to every member of the Society.

Article II—Qualification for Membership

SECTION 1. Applicants for fellowship, associate and corresponding membership approved by the Board of Censors shall be elected by a Ballot of three-fourths of the Fellows voting at any regular meeting.

SEC. 2. Proposal for honorary membership may be made by a Fellow of the Society. Such proposal shall be made in writing and submitted to the Board of Censors. On recommendation by the Board such proposed member shall be elected as provided in Section 1.

Article III—Dues

SECTION 1. All Fellows and Associate Members shall subscribe to this Constitution at the time of their election to membership and shall pay an initiation fee of Ten Dollars ($10.00), payable with the application for membership.

SEC. 2. The annual dues for Fellows and Associate Members shall be Ten Dollars ($10.00), payable December first for the following year and if unpaid on January first the subscription for the official JOURNAL will lapse. Five Dollars ($5.00) of the annual dues shall be used as subscription for the official JOURNAL. New members elected at the annual meeting shall pay dues for the current year of Five Dollars ($5.00) to cover the subscription of the entire volume of the official JOURNAL for that year.

SEC. 3. Fellows in arrears for dues for sixty days shall be notified thereof by the Secretary-Treasurer by means of a "return receipt" registered letter. Fellows in arrears for ninety days shall be automatically dropped from the roll for non-payment of dues. Within one year after loss of membership for non-payment of dues, Fellows may be reinstated upon payment of all arrears and current dues.

SEC. 4. Resignation from the Society shall be submitted in writing to the Secretary-Treasurer who shall cause the same to be presented to the Executive Committee at the next annual meeting and the resignation shall not become effective until acted upon by the Executive Committee. No resignation shall be accepted from a Fellow or member owing dues.

Article IV—Duties of Officers and Standing Committees

SECTION 1. The President shall preside at all meetings of the Society. He shall appoint the Chairman of the Executive Committee and the Chairman of the

Board of Censors, be an ex-officio member of all committees and perform all other duties that devolve on him by custom and parliamentary usage.

SEC. 2. In the absence from any meeting of the Society of the President, the President-Elect and in the absence of both, the Vice-President shall perform the duties of President.

SEC. 3. The President shall appoint the members of all Special Committees enumerated in Article V of these By-Laws except those of the Board of Registry of Technicians. He shall also appoint any additional special committees ordered by the Society and shall be empowered to appoint such others as he may consider necessary and for which he has secured the approval of a majority of the members of the Executive Committee.

SEC. 4. The Secretary-Treasurer shall keep a correct and permanent record of the meetings and the transactions of the Society. He shall furnish a copy of this record to the Editor of the official JOURNAL for publication, conduct the correspondence and perform such other duties as pertain to the office of Secretary. He shall receive and be the custodian of the funds of the Society except the funds of the Board of Registry of Technicians which shall be held by the Chairman of that Board. Within thirty days following the close of the annual meeting he shall present a budget for the ensuing year which shall meet with the approval of a majority of the members of the Executive Committee. He shall incur no additional expense during the year without the consent of a majority of the members of the Executive Committee. He shall give bond satisfactory to the Executive Committee, the cost of which shall be borne by the Society. He shall make a complete financial report at the annual meeting of the Society. He also shall be ex-officio Secretary of the Executive Committee.

SEC. 5. The Executive Committee shall be the executive and administrative body of the Society during the interval between the regular annual meetings and shall be empowered to enter into contracts and authorize such expenditures as may be necessary to carry on the affairs and the business of the Society. Its actions always shall be governed by the Constitution and By-Laws of the Society. It shall audit the accounts of the Secretary-Treasurer as often as it deems necessary and the Chairman shall hold the bonds of the Secretary-Treasurer and the Chairman of the Board of Registry of Technicians. The Committee shall meet prior to the executive session of the Society. The Chairman shall prepare a report to be made to the executive session of the Society on its activities during the interval between the annual meetings and certify to the accounts of the Secretary-Treasurer and the Chairman of the Board of Registry of Technicians. The Committee shall meet also immediately after the annual meeting of the Society to transact such business as properly may come before it.

SEC. 6. The Board of Censors shall investigate all applications for membership and submit their recommendations at the annual meeting of the Society. They shall receive and consider all complaints concerning the conduct of members and present a report at the executive session with their recommendations.

Suspension or expulsion from membership in the Society shall be by three-fourths vote of those members present and voting at a regular executive session.

SEC. 7. The Board of Registry of Technicians shall elect its own Chairman and Secretary. It shall conduct a Registry of Technicians, receive applications for such, pass on their qualifications and issue certificates and renewals of certificates to those meeting the requirements. It shall investigate schools for the training of technicians and register those approved. It shall conduct a placement bureau for technicians. Within thirty days following the close of the annual meeting the Chairman shall present a budget for the ensuing year which shall meet with the approval of a majority of the members of the Executive Committee. He shall incur no additional expense during the year without the consent of a majority of the members of the Board of Registry. The funds of the Registry shall be held by the Chairman of the Board who shall give bond satisfactory to the Executive Committee, the cost of which shall be borne by the Registry. The funds of the Registry shall be used only for the activities of the Registry. The Chairman shall make a complete financial report at the annual meeting of the Society.

Article V—Special Committees and Editor

SECTION 1. A Board of Counselors shall be appointed by the President to serve for one year. They shall represent such districts as may be determined by the President. It shall be the duty of the Counselors to act in the interest of the organization in their respective districts.

SEC. 2. A Nominating Committee of three Fellows shall be appointed by the President at the opening of the annual session, whose duty shall be to prepare a list of nominees for the elective offices for balloting by the Society. Additional nominations may be made from the floor.

SEC. 3. The President shall appoint a Program Committee consisting of three Fellows to serve for one year, the Chairman of which shall be the Secretary of the Society, whose duty it shall be to arrange the scientific program for the annual meeting.

SEC. 4. The President shall appoint a Committee on Exhibits consisting of three Fellows, one of whom shall be the Secretary of the Society, to serve for one year, whose duty shall be to arrange for scientific and commercial exhibits at the annual meeting.

SEC. 5. The President shall appoint a Research Committee consisting of three Fellows, to serve for one year, whose duty it shall be to foster and direct collective investigation and to collect from rare or obscure conditions data and materials to be made available to Fellows for study.

SEC. 6. The Executive Committee shall appoint an Editor for the official JOURNAL of the Society to serve for a term of three years. The Editor so selected together with the President of the Society and the Chairman of the Executive Committee, shall appoint an Advisory Editorial Board to serve for a period of

three years. The duties of this Board shall be to foster and supervise all official publications of the Society.

Article VI—Awards

At each annual session the Research Committee may designate a Fellow of the Society to receive the Ward Burdick Award. This award shall be in the form of a gold medal which shall be presented to that Fellow who, in the opinion of the Research Committee, has presented the most meritorious contributions to the science of clinical pathology. Rules governing the award shall be made by the Research Committee, approved by the Executive Committee and published for the information of Fellows of the Society. If, in the opinion of the Research Committee, at any annual session no contribution is judged of sufficient merit to receive the award, no award shall be made at that session

Article VII—Elections

SECTION 1. The Society shall elect annually by ballot at an executive session at the annual meeting the following officers and members of committees: President-Elect, Vice-President, two Fellows to fill vacancies on the Executive Committee, two Fellows to fill vacancies on the Board of Censors and two Fellows to fill vacancies on the Board of Registry of Technicians and such other vacancies as may have occurred. The Secretary-Treasurer shall be elected in the same manner each third year.

SEC. 2. Election shall be by a majority of votes cast by the Fellows present and shall be from nominees proposed by the Nominating Committee or from nomination made by any Fellow present.

SEC. 3. The President-Elect and newly-elected officers shall be inducted into office at the conclusion of the meeting.

Article VIII—Vacancies

In the event of a vacancy occurring in the office of President, the unexpired portion of his term of office shall be filled by the Vice-President. Vacancies occurring in the offices of Vice-President and Secretary-Treasurer shall be filled for the unexpired term of office by the Executive Committee. If a vacancy should occur in the office of President-Elect, at the next annual meeting the Society shall elect a President in addition to the officers enumerated in Article VII, Section 1 of the By-Laws. Interim vacancies occurring on the Executive Committee, the Board of Censors and the Board of Registry of Technicians shall be filled until the next annual meeting by the Executive Committee.

Article IX—Code of Ethics

SECTION 1. The Code of Ethics of this Society shall be the same as that of the American Medical Association.

SEC. 2. It shall be deemed unethical for members to publish objectionable

laboratory advertisements in any form whatsoever; the Board of Censors shall act as judges in the matter, the members having the privilege of appeal to the Society at a regular executive session.

SEC. 3. It shall be considered unethical for a member to lend his name for publication in any laboratory advertisement or announcement which violates the Code of Ethics. The borrowing of names of other physicians, scientists or laymen, on the basis of an occasional service or consultation, for purposes of advertising or to sanction the work of a laboratory is misleading and unethical.

SEC. 4. Any system of dividing or rebating fees for laboratory services shall be considered unethical.

Article X—Standing Rules

SECTION 1. The Chairman, at all regular annual meetings, shall first call the members assembled to order in executive session for the purpose of transacting such business and appointing such committees as are herein required, together with the making of other arrangements consistent with conducting the annual meeting.

SEC. 2. Scientific papers presented by Fellows shall be limited to twenty minutes; those presented by guests shall not occupy more than thirty minutes. A longer time may be granted only by the consent of a majority of the Fellows present.

SEC. 3. The opening discussion on each paper shall be limited to ten minutes; succeeding discussions shall be limited to five minutes each except as extension of time may be granted by a majority of the Fellows present.

SEC. 4. Members desiring to speak twice on any one subject must obtain the consent of a majority of the Fellows present.

SEC. 5. Non-members may be given the privilege of the floor only by consent of the majority of the Fellows present.

SEC. 6. A paper read before this Society becomes the property of the Society, to be published in the official JOURNAL provided it meets the approval of the Advisory Editorial Board, except that the privilege for prior publication may be granted by the Editor.

SEC. 7. Order of Business for Executive Session:

1. Call to order.
2. Reading of minutes.
3. Unfinished business.
4. Reports of committees.
5. Election of members.
6. New business.
7. Nominations.
8. Election of officers.
9. Induction of officers.
10. Adjournment.

Article XI—Parliamentary Procedure

All parliamentary proceedings at the meetings of this Society shall be governed by Roberts' Rules of Order, except where otherwise provided.

Article XII—Amendments

Amendments of these By-Laws must be submitted in writing at the opening of the annual meeting and shall be voted upon at the executive business session. A majority of the votes cast shall be required to amend.

THE AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS ROSTER FOR 1934

Officers

Dr. Frederick H. Lamb.....President
Dr. Benjamin S. Kline.....Vice-President
Dr. Foster M. Johns.....President-Elect
Dr. Alfred S. Giordano.....Secretary-Treasurer

Executive Committee

Dr. Alvin G. Foord, Chairman
Dr. K. Ikeda
Dr. W. M. Simpson
Dr. H. C. Sweany
Dr. H. J. Corper
Dr. C. I. Owen

Past Presidents

1922–3	Dr. Philip Hillkowitz.....	Denver, Colorado
1923–4	Dr. Wm. Carpenter MacCarty.....	Rochester, Minnesota
1924–5	Dr. John A. Kolmer.....	Bala-Cynwyd, Pa.
1925–6	Dr. Frederic E. Sondern.....	New York, N. Y.
1926–7	Dr. Wm. G. Exton.....	New York, N. Y.
1927–8	Dr. A. H. Sanford.....	Rochester, Minnesota
1928–9	Dr. F. W. Hartman.....	Detroit, Michigan
1929–30	Dr. J. H. Black.....	Dallas, Texas
1930–1	Dr. K. M. Lynch.....	Charleston, S. C.
1931–2	Dr. H. J. Corper.....	Denver, Colorado
1932–3	Dr. Walter M. Simpson.....	Dayton, Ohio
1933–4	Dr. Alvin G. Foord.....	Pasadena, California

Members of the American Society of Clinical Pathologists

Geographic Distribution

* Associate Members.
† Counsellors.
§ Corresponding Members.
** Honorary Members.

FOREIGN

**Achard, Charles.....Academy of Medicine, Paris, France
Bates, Lewis B.....Gorgas Hospital, Ancon, Canal Zone
Bauer, J. A.....238 Main St., E., Hamilton, Canada
Costa-Mandry, Oscar G.....Box 536, San Juan, Porto Rico
Deadman, Wm. James.....General Hospital, Hamilton, Ontario, Canada
de Leon, Walfrido.....Kansas Avenue 609, Manila, Philippine Islands
**Dodds, E. C.....Middlesex Hospital, London, W. I.
§Dyke, S. C.....9 George St., Wolverhampton, England
Fennel, Eric A.....The Clinic, Honolulu, Hawaii
McCants, J. M.....Submarine Base, Coco Solo, Canal Zone
§ Miloslavich, E. L.....University of Zagreb, Agram, Jugoslavia
**Naegeli, Otto.....Zurich University, Zurich, Switzerland
Reuter, C. H.....Kahului, Hawaii

ALABAMA

†Graham, G. S.....Medical Arts Bldg., Birmingham, Ala.
Trumper, Abraham.....226–228 Bell Building, Montgomery, Alabama
Jones, W. C.....Employees Hospital, Fairfield, Alabama

ARKANSAS

†Lee, D. C.....503 Medical Arts Bldg., Hot Springs, Ark.

CALIFORNIA

Andrews, V. L.....6025 Carlton Way, Hollywood, Calif.
Ball, Howard A.....4643 El Cerrito Drive, San Diego, California
Bettin, M. E.....727 West 7th St., Los Angeles, California
Bogen, Emil.....Olive View Sanitarium, Olive View, Calif.
Bolin, Zera E.....450 Sutter Street, San Francisco, Calif.
Bonynge, C. W.....1930 Wilshire Blvd., Los Angeles, Calif.
Case, Lucius W.....131 Lincoln Avenue, Pomona, California
Cummins, W. T.....975 Bush St., San Francisco, Calif.
Elliott, Frances P.....1028—32nd St., San Diego, California
Evans, Newton.....1100 N. Mission Road, Los Angeles, California
Foord, Alvin G.....Pasadena Hospital, Pasadena, California
Glenn, Robert A.....Samuel Merritt Hospital, Oakland, Calif.
Hammack, Roy W.....657 S. Westlake Ave., Los Angeles, Calif.
Holliger, Charles D.....203 Medico-Dental Bldg., Stockton, Calif.
†Hyland, C. M.....4614 Sunset Blvd., Los Angeles, Calif.
Kosky, Alfred A.....509 21st Place, Santa Monica, California
Lindberg, A. L.....1407 S. Hope St., Los Angeles, Calif.
Maner, G. D.....523 W. 6th St., Los Angeles, Calif.
Marquez, H. G.....Flood Bldg., San Francisco, Calif.
Moore, Gertrude.....2404 Broadway, Oakland, Calif.
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Easton, Pennsylvania

REGISTRY OF TECHNICIANS

In view of the encouragement given by the American College of Surgeons to have all technicians of approved hospitals apply for certificates from the Registry, a large number of new applicants have taken the October examinations.

At the meeting of the Board of Registry held in Cleveland, during the convention of the American Society of Clinical Pathologists, considerable business was transacted, the most important being

1. Examination of applications of 24 candidates for rating of Medical Technologist. Fifteen were rejected and nine approved.

2. Consideration of the applications of 16 training schools for approval and registration. Two of them were approved, ten rejected, and four were held over pending the joint action of the Board and the Council on Medical Education and Hospitals of the American Medical Association, which will be taken within the next year to unify the standards of hospital training course for laboratory technicians. The final action must necessarily await the completion of inspection of training schools throughout the United States by the inspectors of the Council.

3. Decision to publish in our official JOURNAL the examination questions and the names of those who successfully passed the examination.

4. Re-emphasis on the decision that no technician shall be granted a certificate of registration who operates a private laboratory "regardless of location."

5. Decision to the effect that after 1936 the minimum requirements for registration of laboratory technicians shall be raised to two years of college work including major sciences. The technicians who meet the minimum requirements of one year college including chemistry and biology and who shall have completed their training prior to 1936, are eligible to register after 1936. The credits submitted should be verified through the state board of education or other authorized educational agent before the student is enrolled.

An informal conference was held by the members of the Board and Doctor Cutter of the Council on Medical Education and Hospitals of the A. M. A. and members of his staff. It was decided to formulate the essentials for approval of training schools for laboratory technicians by the joint action of the Council and the Board as soon as inspection of a sufficient number of the training schools has been completed by the Council's representatives during the coming year. It is the desire of the Council to coöperate with the Board in this

undertaking and not to supplant the Board or duplicate the program of the Board in this matter. In the future, any action to be taken by the Board with reference to approval of training schools for laboratory technicians is to be referred to the Council for its approval and endorsement. Eventually approval of these schools will be granted only by the joint action of the Council and the Board, according to the minimum requirements or essentials to be formulated jointly.

The JOURNAL calls attention with a great deal of pride to the increase in advertising in its pages. It is a particular pleasure to call attention to the advertisements of the Corning Glass Company, Research Supply Corporation, Loeser Laboratories, Reiker Instrument Company, and Central Scientific Company. While some of these organizations have been advertisers in the past, they have recently renewed their contracts with the JOURNAL. Members of the Society will find these high class firms ready to supply them with good laboratory material. In ordering supplies from these and our other advertisers, we urge you to refer to the JOURNAL.

American Journal of Clinical Pathology

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(Examples) Kolmer, J. A.: Toxin production by *Spirochaeta pallida*. Arch. Derm. and Syph., 20: 189–190. 1929.

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